L Number	Hits	Search Text	DB	Time stamp
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3	1	("4994071").PN.	USPAT; US-PGPUB; EPO; JPO	2004/01/25 19:50
4	1	("4916193").PN.	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:07
5	370	stent same hydrogel same (bioerod$ bioabsorb$ biosorb$ biodegrad$)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:08
6	284	stent same hydrogel with (bioerod$ bioabsorb$ biosorb$ biodegrad$)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:22
7	31	stent same polyethylene adj (oxide glycol) with (bioerod$ bioabsorb$ biosorb$ biodegrad$)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:09
8	284	(stent same hydrogel with (bioerod$ bioabsorb$ biosorb$ biodegrad$)) and (drug medicament therapeutic agent)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:22
9	1089	hydrogel near3 (bioerod$ bioabsorb$ biosorb$ biodegrad$)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:22
10	343	(hydrogel near3 (bioerod$ bioabsorb$ biosorb$ biodegrad$)) and (drug and stent)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:22
11	183	((hydrogel near3 (bioerod$ bioabsorb$ biosorb$ biodegrad$)) and (drug and stent)) and coat	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:30
12	1316	hydrogel with (polyethylene adj (oxide glycol))	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:31
14	56	(hydrogel with (polyethylene adj (oxide glycol))) same stent	USPAT; US-PGPUB; EPO; JPO	2004/01/25 20:31
15	28	larson.in. with (marian eugene)	USPAT; US-PGPUB; EPO; JPO	2004/01/25 21:32

US005302399A

United States Patent [19]

Otagiri et al.

[11] Patent Number: 5,302,399

[45] Date of Patent: Apr. 12, 1994

[54] SLOW-RELEASING PHARMACEUTICALS PREPARED WITH ALGINIC ACID

[75] Inventors: Masaki Otagiri; Teruko Imai, both of Kumamoto, Japan

[73] Assignee: Snow Brand Milk Products Co., Ltd., Sapporo, Japan

[21] Appl. No.: 852,624

[22] Filed: Mar. 12, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 444,161, Nov. 9, 1989, abandoned.

[30] Foreign Application Priority Data

Mar. 9, 1988 [JP] Japan 63-055784
Sep. 2, 1988 [JP] Japan 63-219747

[51] Int. Cl.[5] A61K 9/62
[52] U.S. Cl. 424/493; 424/489; 424/499
[58] Field of Search 424/489, 491, 492, 493

[56] References Cited

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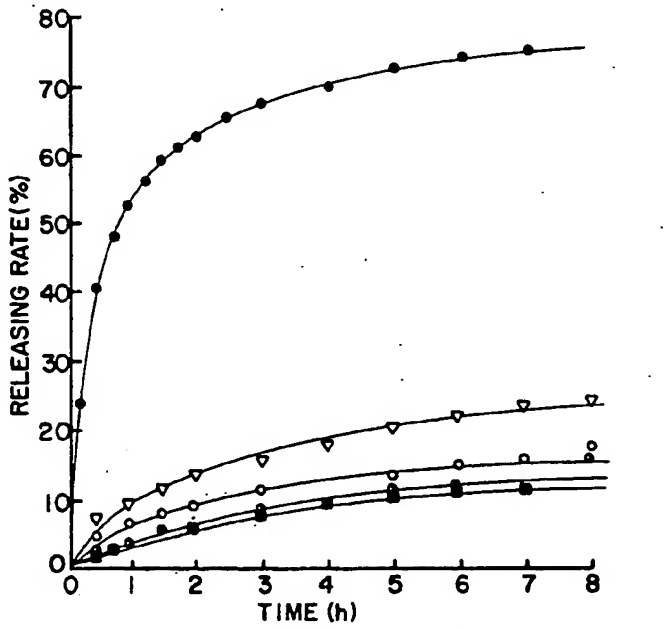
Primary Examiner—Thurman K. Page
Assistant Examiner—Neil Levy
Attorney, Agent, or Firm—Millen, White, Zelano, & Branigan

[57] ABSTRACT

A slow-releasing pharmaceutical easily prepared with alginic acid gel beads as a slow releasing carrier, and a basic medicament such as a beta-blocking agent or a calcium antagonistic agent therein, whereby the basic medicament can be relesed at a desired rate by means of oral administration, etc.

12 Claims, 7 Drawing Sheets



●:PINDOLOL ADMINISTERED IN POWDER FORM
▽:PINDOLOL ADMINISTERED IN ULA ALGINIC ACID GEL BEADS
○:PINDOLOL ADMINISTERED IL$_2$ ALGINIC ACID GEL BEADS
◎:PINDOLOL ADMINISTERED IN MA ALGINIC ACID GEL BEADS
■:PINDOLOL ADMINISTERED IN DA-20 ALGINIC ACID GEL BEADS

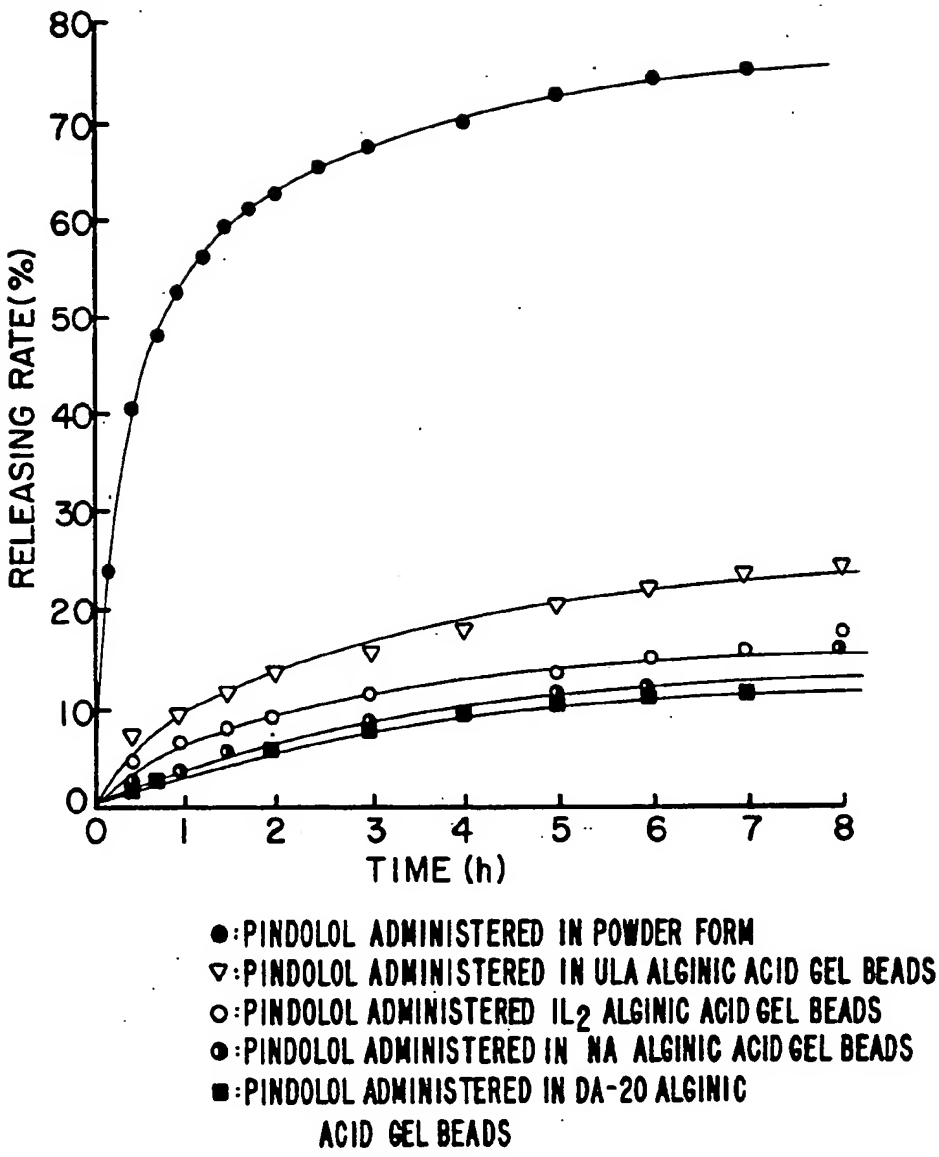
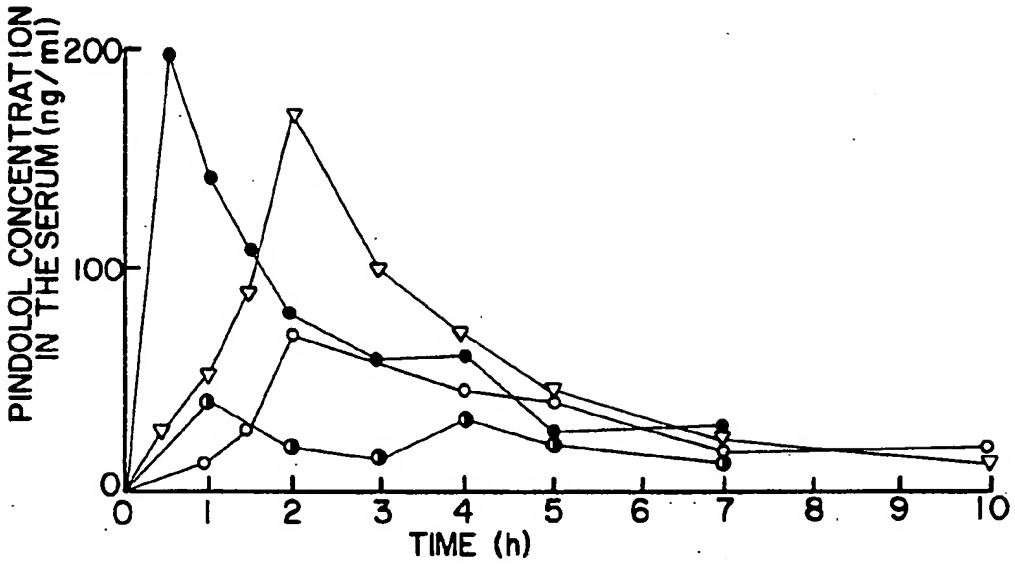

RELEASING RATE(%)
TIME (h)
0
10
20
30
40
50
60
70
80
0
1
2
3
4
5
6
7
8
●:PINDOLOL ADMINISTERED IN POWDER FORM
▽:PINDOLOL ADMINISTERED IN ULA ALGINIC ACID GEL BEADS
○:PINDOLOL ADMINISTERED IL2 ALGINIC ACID GEL BEADS
◐:PINDOLOL ADMINISTERED IN NA ALGINIC ACID GEL BEADS
■:PINDOLOL ADMINISTERED IN DA-20 ALGINIC ACID GEL BEADS

FIG. 1



○: PINDOLOL ADMINISTERED IN POWDER FORM
▽: PINDOLOL ADMINISTERED IN ULA ALGINIC ACID GEL BEADS
○: PINDOLOL ADMINISTERED IN IL_2 ALGINIC ACID GEL BEADS
●: PINDOLOL ADMINISTERED IN NA ALGINIC ACID GEL BEADS

FIG. 2

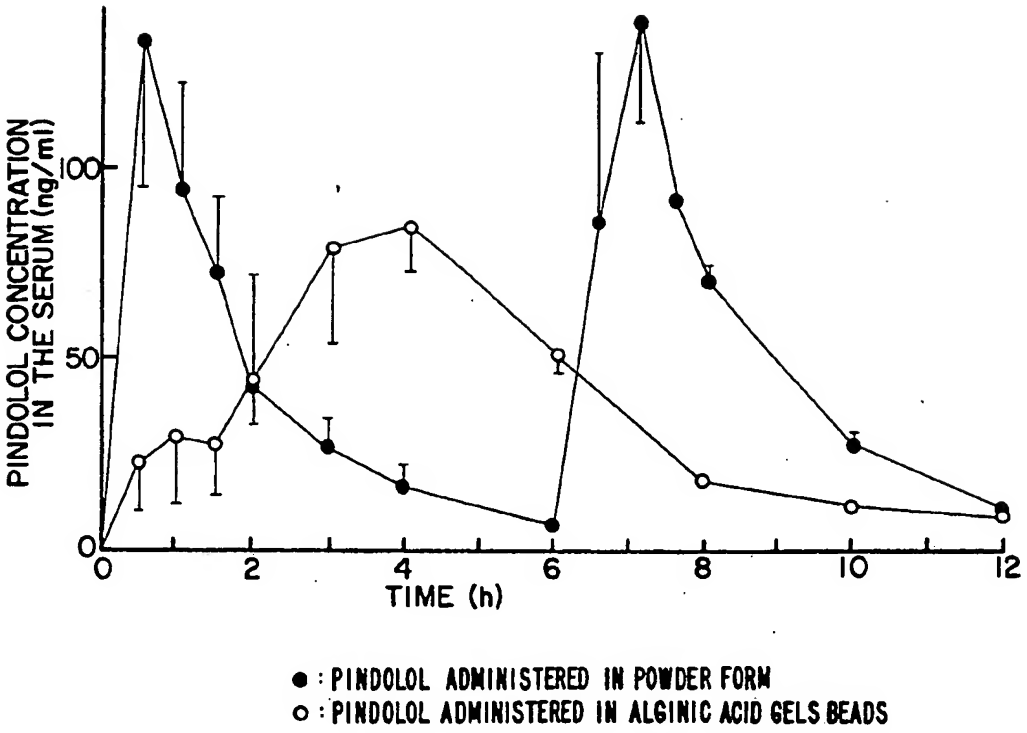
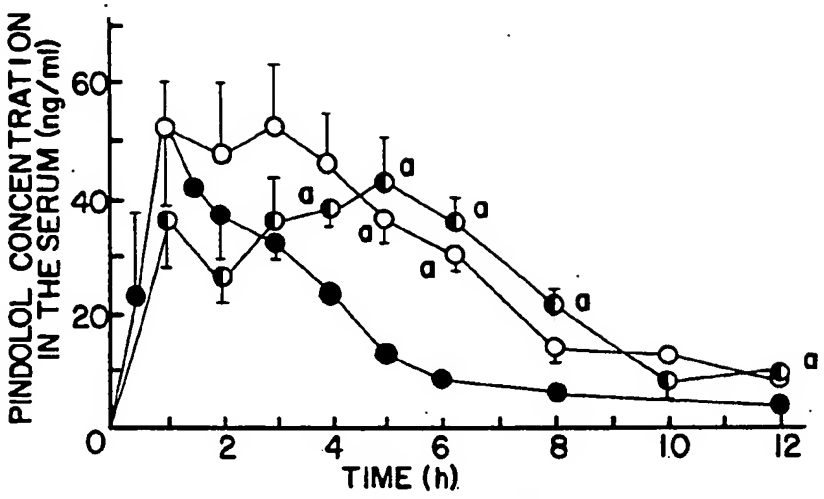
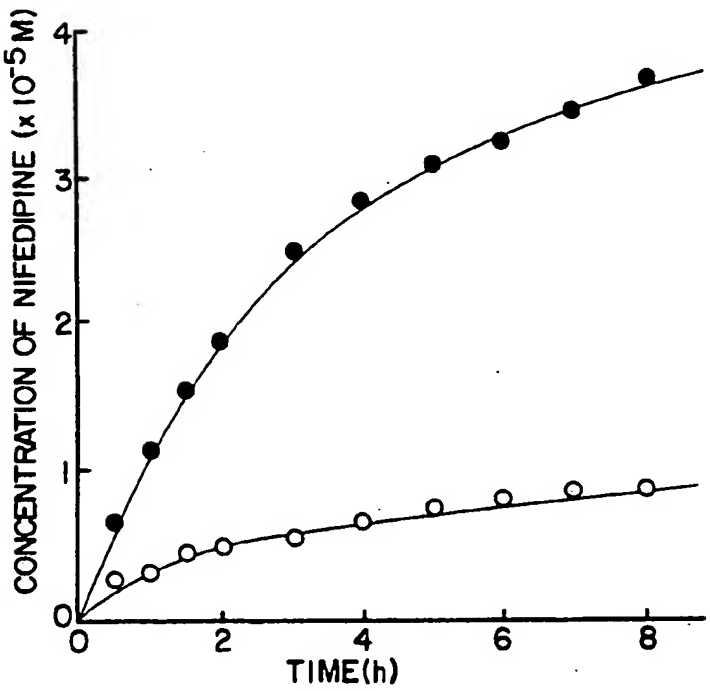

PINDOLOL CONCENTRATION IN THE SERUM (ng/ml)
100
50
0
0
2
4
6
8
10
12
TIME (h)
● : PINDOLOL ADMINISTERED IN POWDER FORM
○ : PINDOLOL ADMINISTERED IN ALGINIC ACID GELS BEADS

FIG. 3



●: PINDOLOL ADMINISTERED IN POWDER FORM
◐: PINDOLOL ADMINISTERED IN CALVISKEN R
○: PINDOLOL ADMINISTERED IN ALGINIC ACID GEL BEADS
a: $P < 0.05$ TO POWDERED PINDOLOL

FIG. 4



●: NIFEDIPINE IN POWDER FORM
○: NIFEDIPINE IN ALGINIC ACID GEL BEADS

FIG. 5

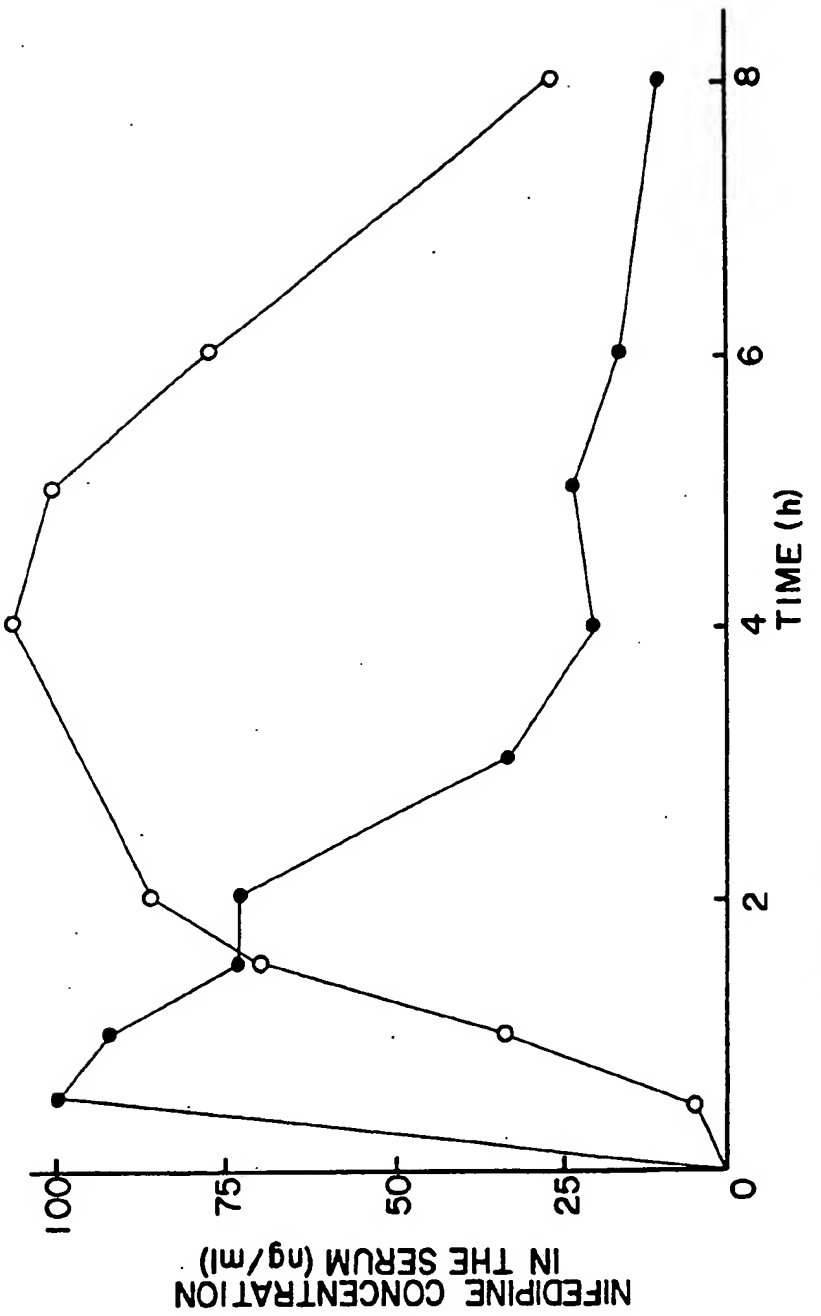
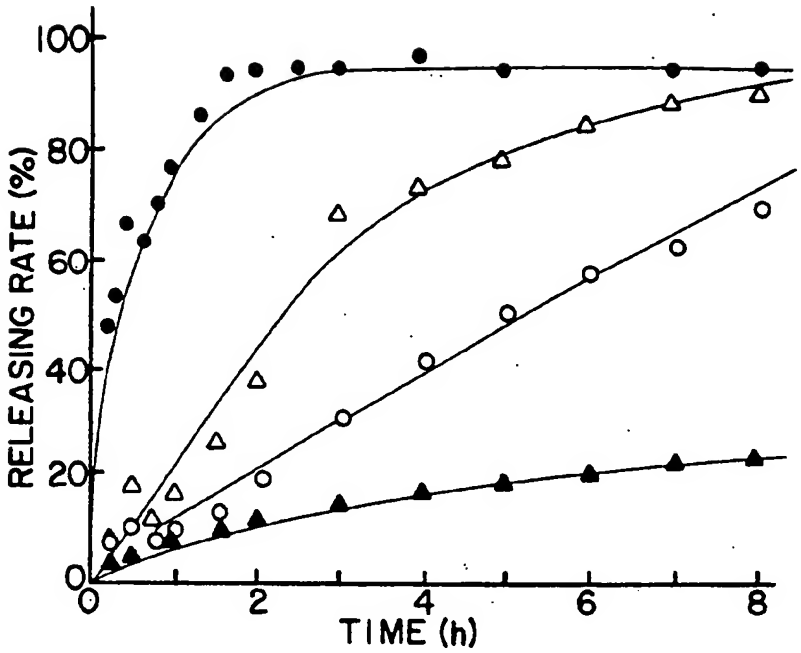

NIFEDIPINE CONCENTRATION
IN THE SERUM (ng/ml)
100
75
50
25
0
2
4
6
8
TIME (h)
●: POWDER FORM
○: GEL BEADS

FIG. 6



● : PINDOLOL IN POWDER FORM
▲ : PINDOLOL IN ALGINIC ACID GEL BEADS
M/C RATIO = 0.53
○ : PINDOLOL IN ALGINIC ACID GEL BEADS
M/C RATIO = 1.3
△ : PINDOLOL IN ALGINIC ACID GEL BEADS
M/C RATIO = 2.4

FIG. 7

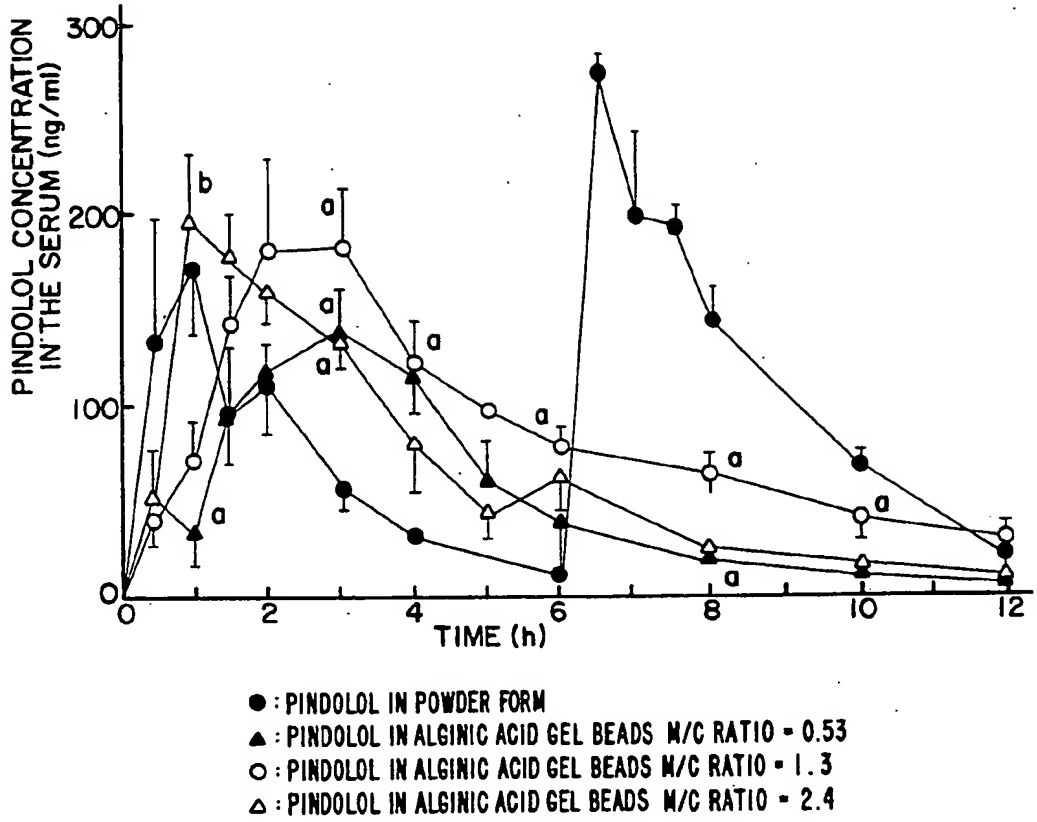

PINDOLOL CONCENTRATION IN THE SERUM (ng/ml)
300
200
100
0
0
2
4
6
8
10
12
TIME (h)
b
a
a
a
a
a
a
a
a
a
● : PINDOLOL IN POWDER FORM
▲ : PINDOLOL IN ALGINIC ACID GEL BEADS M/C RATIO = 0.53
○ : PINDOLOL IN ALGINIC ACID GEL BEADS M/C RATIO = 1.3
△ : PINDOLOL IN ALGINIC ACID GEL BEADS M/C RATIO = 2.4

FIG. 8

SLOW-RELEASING PHARMACEUTICALS PREPARED WITH ALGINIC ACID

This is a continuation of application Ser. No. 07/444,161, filed Nov. 9, 1989, abandoned.

FIELD OF THE INVENTION

This invention relates to a slow-releasing pharmaceutical in which a basic medicament is contained in alginic acid gel beads and to a method for the production of the same.

DESCRIPTION OF THE PRIOR ART

Recently, the preparations of slow-releasing pharmaceuticals have been designed for the purpose of improving effectiveness and the safety of medicaments since slow-releasing pharmaceuticals reduce the number of doses, retain the expression of specified effects or reduce the incidence of side effects or toxicity as compared to ordinary fast-releasing pharmaceuticals.

Regarding these slow-releasing pharamaecuticals, in order to control the rate of release of medicaments in the body, various pharmaceuticals forms such as microcapsules, nano-capsules and matrices using various natural polymers, synthetic polymers, synthetic elastomers or the like have been suggested. For example, Shigeru Goto and Masakazu Kawada ("New Pharmaceutical Development System General Technology Design" R&D Planning Company, p.140, 1986) disclosed preparation of microcapsules or nano-capsules. Furthermore, matrix preparations have been disclosed by M. Bamba et al. (Int. J. Pharmaceut., 2307, 1979) and F. A. Kincl et al. (Archiv. Pharm., 317, 1984) and R. V. Sparer et al. (J. Contr. Release, 1, 23, 1984).

However, these preparations have problems such that the choice of combinations of medicaments and polymers and the processes employed for the preparation of slow-releasing pharmaceuticals thereby are complex.

The present inventors found that a pharmaceutical having a sufficiently slow-releasing property can be obtained by such simple means that a basic medicament is contained in alginic acid gel beads prepared with a polysaccharide, alginic acid which is a kind of natural polymer and a constituent of the cell membrane of brown algae.

Further, alginic acid is commercially available in forms of sodium salts having various molecular weight. Since alginic acid is slowly dissolved in water and highly viscous, it is used as a stabilizer or viscous agent in viscous foods such as ice cream, cheese, sherbet and syrup and also used in manufacturing films and fabrics.

SUMMARY OF THE INVENTION

Objects of the present invention are to provide a pharmaceutical form of a basic medicament having desirable slow-releasing properties using alginic acid gels, and to provide a method for the preparation of the same.

A slow-releasing pharmaceutical of the present invention is characterized by including a basic medicament in an acidic alginic acid gel beads so as to provide preferable binding features and to give preferable slow-releasing effects.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the release of pindolol from the alginic acid gel beads in Example 1. FIG. 2 shows the change in the serum pindolol concentration after oral administration of the alginic acid gel beads to rabbits. FIG. 3 shows the change in the serum pindolol concentration after oral administration f the alginic acid gel beads to beagle dogs. FIG. 4 shows the absorption of pindolol in the alginic acid gel beads in beagle dogs.

FIG. 5 shows release f nifedipine from the alginic acid gel beads in Example 2. FIG. 6 shows the absorption of nifedipine contained in alginic acid gel beads.

Furthermore, FIG. 7 shows the releasing effect of alginic acid gel beads with the M/G ratio of 1:3 as compared to alginic acid gel beads with other M/G ratios. FIG. 8 shows the change of the scrum pindolol concentration in beagle dogs orally administered with pindolol powder and with alginic acid gel beads with the same M/G ratio as above.

DETAILED DISCLOSURE

Examples of the basic medicaments used in the present invention include beta-blocking agents such as pindolol, procaterol, propranolol, pyltelol, and befunolol; calcium antagonists such as nifedipine, verapamil, diltiazem, and nicardipine; antihistamine agents such as difenhydramine, diphenylpyraline and chlorophenylamine; diuretics such as triamterene and penflutizide, vasodilative agents such as cinnarizine, ifenprodil, and pentoxifylline; and antitusives such as eprazinone, chloroprenaline, chloperastine, trimethoquinol, bromhexine, methoxyphenamine and sulbutanol.

In the present invention, alginic acid gel beads containing the above basic medicaments can be prepared using commercially available sodium alginates. However, in order to accomplish continuous and appropriate release of medicaments, particularly, sodium alginates having a molecular weight of about 10,000–100,000 are preferably used. 1% solutions of such sodium alginates have a viscosities of less than 100 cps and are useful in designing a preferable releasing system by selecting suitable sodium alginate depending on the kinds of medicament and releasing patterns.

In the present invention, alginates having the following features were used.

Sodium alginate	MM/GG	Viscosity (cp)
No. 1	0.13	13.3
No. 2	0.66	13.7
No. 3	1.77	12.1

Consequently, as for the alginic acid gel, it has been determined that the release of the above-mentioned medicaments are affected by the difference in the ratio (M/G ratio) of constituent sugars of the alginic acid, i.e., mannouronic acid (M) and guluronic acid (G). Further, it has also been revealed that the above-mentioned release is affected by the ratio of homo-block (MM) of mannuronic acid (M) and homo-block (GG) of guluronic acid (G) and furthermore the viscosity of alginic acid. Herein, the homo-block (MM, GG) means a block in which the same uranic acid (M or G), is sequenced.

In other words, when the amount of guluronic acid in the sugar composition increases, the matrix becomes so dense that the release of a medicament in the alginic acid gel beads becomes difficult. Also, when the MM/GG ratio is small, for example 0.13, the medicament can be released slowly.

According to the present invention, alginic acid gel beads which contain a basic medicament can be prepared as follows:

A basic medicament is suspended in a 4% sodium alginate solution and added drop by drop through a nozzle to a 0.1M $CaCl_2$ solution. The solution is allowed to stand for 72 hours and then alginic acid gel beads containing the basic medicament are collected by filtration. The alginic acid gel beads are dried in air for 24 hours and then dried in vacuo at room temperature for 24 hours.

In the above process, the molecular weight of the sodium alginate greatly affects both the yield of alginic acid gel beads formed and the content of the medicament contained in the alginic acid gel beads. With a view to controlling the release, alginic acid having a low viscosity, i.e. a low molecular weight, is preferably used.

Prior to preparation, the concentration of the basic medicament should be determined by considering the amount necessary to achieve the desired release.

According to the present invention, the alginic acid gel beads containing a basic medicament, thus obtained, can be formulated as necessary, for example, into enteric coated pills.

Further, a pharmaceutical according to the present invention can be expected to control the absorption of sodium in the body, since alginic acid forms gel structures by binding to calcium and thus calcium is replaced by sodium when the alginic acid is diffused to release the medicament therefrom in the intestine.

A process for the preparation of the slow-releasing pharmaceutical of the present invention and releasing effects of the same are explained more in detail by the following Examples.

EXAMPLE 1

Preparation of Alginic Acid Gel Beads

As a basic medicament, a beta-blocking agent, pindolol, was suspended in a 4% sodium alginate solution (M/G ratio of alginic acid=0.6) to make a pindolol concentration to 4% and the resultant suspension was added drop by drop using a nozzle into a 0.1M $CaCl_2$ solution. The resultant mixture was allowed to stand for 72 hours so as to prepare alginic acid gel beads containing pindolol therein.

The gel beads thus obtained were collected by filtration, dried in air for 24 hours and then dried in vacuo for 24 hours at room temeprature. The resultant preparation was subjected to a medicament releasing test, oral administration tests in rabbits or beagle dogs and an absorption test of the medicament in humans.

The sodium alginates used were as follows:

(1) A product of Kimizu Chemicals, sodium alginate with low viscosity (IL_2), the viscosity of a 1% solution: 20–50 cps;

(2) A product of Kimizu Chemicals, sodium alginate of ultra low viscosity (ULA), the viscosity (10% solution): 500 cps;

(3) A product of Wako Pure Chemicals, reagent grade sodium alginate (NA), the viscosity (1%): 20 cps; and

(4) A product of Kibun Food Chemipha, Dack alginic acid (DA-20), the viscosity (1%): 20 cps.

Further, the pindolol content and yield in alginic acid gel beads are shown in Table 1.

TABLE 1

	Pindolol (%)	Recovery (%)
NA	47.2	78.9
IL_2	44.9	75.8
ULA	14.5	21.5
DA-20	60.2	77.5

Medicament Releasing Test

Alginic acid gel beads containing 10 mg of pindolol as pindolol were suspended in 150 ml of water maintained at 37° C. The suspension was stirred at 150 rpm and the medicament released was measured at given intervals.

As shown in FIG. 1, the rate of the release of pindolol was much slower from the alginic acid gel beads than from pindolol by itself. Furthermore, the lower the viscosity of sodium alginate used (i.e., the smaller the degree of polymerization of alginic acid), the better was the release of pindolol.

Oral Administration Test in Rabbits

Male Japanese white rabbits (2.0–2.5 kg) were starved for 24 hours before the administration of medicaments.

alginic acid gel beads (30 mg/kg as pindolol) was administered with 100 ml of the alginic acid gel beads to the test animals and 3 ml of blood sample was taken from the auricular veins of each animals at given intervals. The samples were centrifuged and 1 ml each of serum was obtained. Pindolol was extracted from the serum and was quantatively measured by high performance liquid chromatography (HPLC).

As shown in FIG. 2, the pindolol concentration transferred to the serum after the oral administration to the rabbits was lower in the case of administration of pindolol as alginic acid gel beads than as pindolol by itself. As evident from the results, pindolol contained in the alginic acid gel beads was absorbed slowly, which showed slow-releasing effects. Moreover, the higher the viscosity of alginic acid, the smaller were the rate and amount of pindolol absorption. Consequently, it is considered that the pindolol concentration in the serum can be controlled by the combination of various kinds of alginic acid gel beads.

Oral Administration Test Using Beagle Dogs

Male beagle dogs (10 kg) were starved for 24 hours before the adminsitration of a test medicament. Water was given ad libitum.

In the case of the administration of pindolol by itself, a total amount 5 mg/kg of a powdered medicament was administered, i.e. 2.5 mg/kg with 20 ml of water at the start and 6 hours later. In the case of the administration of pindolol contained in alginic acid gel beads, 5 mg/kg was orally administered with 20 ml of water. Water was given ad libitum during the test period. At given intervals, 5 ml of blood was taken from the forefoot vein and centrifuged so as to obtain 2 ml each of the serum. The medicament was extracted from the serum and quantatively determined by high performance liquid chromatography (HPLC).

In this test, alginic acid gel beads prepared using the 1 w viscosity alginic acid gel beads (IL_2, Kimizu Chemicals) were used.

Results are shown in FIG. 3.

Further, the results of the velocity analysis of the concentration of the medicament in the serum are shown in Table 2.

TABLE 2

Form of preparation and time elaspsed	AUC (ngh/ml)	MRT (h)	VRT (h^2)
Pindolol powder			
0 → 6 h	238.0	1.74	1.74
0 → 12 h	311.4	1.98	1.83
Alginic acid gel beads			
0 → 12 h	445.7	4.62	5.93

AUC: Concentration in the serum - Area under the time curve
MRT: Mean retention time (average time in which the medicament retain in the body; the faster the absorption, the smaller the value of MRT.)
VRT: Variance of retention time (the longer the retention, the larger the value of VRT).

The results of this analysis revealed that pindolol contained in the alginic acid gel beads was absorbed more slowly and moreover retained activity longer than pindolol by itself. Namely, the slow-releasing effect by the use of alginic acid gel beads was observed.

Absorption Test in Humans

The alginic acid gel beads (alginic acid having MM/GG=0.66 was used) that was revealed to be the most advantageous slow-releasing pharmaceutical in the oral administration test mentioned above were orally administered to four healthy human adults and compared with a commercially available pindolol slow-releasing pharmaceutical, Calvisken (registered trademark, Sankyo Co., Ltd.). Calvisken is a release-retaining nucleated double-layered tablet in which 10 mg each of pindolol is contained in the core tablet and in the outer layer and the enteric coat is coated on the core tablet.

FIG. 4 shows the change of pindolol concentration in the serum (figures are the average±standard deviation for the 4 adults). In the case where powdery pindolol was orally administered in an amount of half (10 mg) of the slow-releasing pharmaceutical, T_{max} (time to reach the maximum serum concentration) was about 1 hour and the medicament in the serum was thereafter gradually disappeared. On the other hand, in the case of the two kinds of the slow-releasing pharmaceuticals, for 1 to 6 hours after the administration, the pindolol concentration in the serum was maintained comprative to C_{max} (maximum serum concentration) after the administration of powdery pindolol; thus it was confirmed that the alginic acid gel beads was biologically equivalent to calvisken R. Since the effective concentration of pindolol in the serum is 10–50 ng/ml, in the case of the alginic acid gel beads, the serum pindolol concentration is rather exceedingly high for 3 hours after the administration. However, the effective pindolol concentration in the serum was maintained for 10 hours after the administration. Velocity parameters obtained by the analysis of the change in the concentration in the serum are shown in Table 3.

TABLE 3

Form of preparation	AUC (ng h/ml)	MRT (h)	VRT (h^2)
Pindolol powder	377.5 ± 48.5*	3.82 ± 0.32	7.44 ± 0.54
Alginic acid gel beads	336.3 ± 43.3**	4.66 ± 0.42[a)]	8.16 ± 0.47
Calvisken R	305.7 ± 25.7**	5.07 ± 0.30[a)]	7.49 ± 0.37

Note:
*$AUC_{0-6} \times 2$
**AUC_{0-12}
[a)] $p < 0.05$ to the value for powdery pindolol (Significantly different from that for powdery pindolol at the significance level of 5%)

As shown in Table 3, the AUCs after the administration of the slow-releasing pharmaceuticals were slightly smaller than the 2-fold of the AUC after the administration of powdery pindolol; but significant difference was not observed. Furthermore, the MRT for the slow-releasing pharmaceuticals is longer than that for the powdery pindolol; thus, the slow releasing effect was confirmed.

Consequently, it was clear that the alignic acid gel beads prepared according to this example were as effective as the commercially available slow-releasing tablet, Calvisken R; thus the usefulness of the alginic acid as a slow-releasing carrier was confirmed.

EXAMPLE 2

Preparation of Alginic Acid Gel Beads

As a basic medicament, a calcium antagonist, nifedipine, was suspended in a 4% low viscosity sodium alginate solution (IL_2, Kimizu Chemicals) to make a pindolol concentration to 4% and then the suspension was added drop by drop using a nozzle into a 0.1M $CaCl_2$ solution. The resultant mixture was allowed to stand for 72 hours so as to prepare alginic acid gel beads containing nifedipine.

The content of nifedipine in the gel beads thus obtained was 45%.

The gel beads were collected by filtration, dried in air for 24 hours and then dried in vacuo for 24 hours at room temperature. The resultant preparation was subjected to the medicament releasing test.

Medicament Releasing Test

The alginic acid gel beads corresponding to 10 mg as nifedipine were suspended in 150 ml of water maintained at 37° C. The suspension was stirred at 150 rpm and the medicament released was measured at given intervals.

As shown in FIG. 5, the rate of the release of nifedipine was much slower from the alginic acid gel beads than from nifedipine by itself.

Absorption Test in Beagle Dogs

The oral administration to beagle dogs was carried out in the same manner as described in Example 1 using pindolol. The nifedipine concentration in the serum was determined in the same manner as described in Example 1.

As shown in FIG. 6, nifedipine contained in the alginic acid gel beads was absorbed more slowly and more extensively than pindolol in powder form.

EXAMPLE 3

This example is carried out to demonstrate the effect of the ratio of mannuronic acid and guluronic acid (M/G ratio) in the constituent sugar in alginic acid used for alginic acid gel beads on the slow releasing effect of a medicament.

Preparation f Alginic Acid Gel Beads

Sodium alginates having the M/G ratios of 0.5, 1.3 and 2.4 were used. Alginic acid gel beads were individually prepared in the same manner as described in Example 1.

Then, the alginic acid gel beads thus btained were subjected to the medicament releasing test according to the procedure described in Example 1 to investigate the releasing pattern of pindolol. As shown in FIG. 7, it was revealed that at the M/G ratio=1.3, the rate of the release of pindolol was appropriately controlled. Moreover, the oral administration test using beagle dogs was carried out in the same manner as in Example 1 so as to investigate the change in the concentration of pindolol in the serum. Results are shown in FIG. 8. As shown in FIG. 8, the advantage of the use of the alginic acid gel beads prepared using alginic acid having the M/G ratio=1.3 was observed.

Possible Industrial Use

A slow-releasing pharmaceutical of the present invention can be prepared containing a basic medicament in alginic acid gel beads, in which the M/G ratio, MM/GG ratio and the molecular weight of the alginic acid to be used are selected depending on the desired releasing rates and, furthermore, alginic acid gel beads having an appropriate matrix structure are easily prepared using a metal ion such as Ca ion or the like for the alginic acid gel formation. As a result, a pharmaceutical which exerts the desirable effect of slow-releasing of effective ingredients can be prepared.

Furthermore, since the pharmaceutical of the present invention exerts the slow-releasing effect also by ordinary oral administration, it is extensively applicable in the field of medicine. In particular, it is extremely useful in the field where retention of the effect of efficacious ingredients and reduction in the number of dose are desirable or in the field where manifestation of side effects or toxicity due to prompt effectiveness is apprehended.

Furthermore, the slow releasing pharmaceutical prepared with the alginic acid gel beads according to the present invention is extensively applicable in various kinds of chemical reactions as a catalyst or additive. Furthermore, the alginic acid gel beads are widely applicable to a fertilizer, agricultural chemical, soil chemicals, food additive or the like because the gel beads can be easily formulated into various forms.

I claim:

1. In a process for the production of alginate gel beads containing a particulate bioactive material dispersed therein by the steps f adding a solution of a water soluble salt of alginic acid which contains the bioactive material dispersed therein dropwise into a solution of gellant for the alginic acid, thereby producing the beads and then separating and drying the thus-produced beads, the improvement which comprises the combination of employing as the bioactive material a suspension in the starting solution of particles of a basic medicament adapted for oral ingestion; employing $CaCl_2$ as the gellant; and employing as the starting solution of a water soluble salt of alginic acid, a 4% solution of the sodium salt of an alginic acid which has a molecular weight of about 10,000–100,000 , a ratio of homo-block (MM) mannuronic acid to homo-block (GG) guluronic acid therein of from 0.13 to 1.77 and a viscosity, as a 1% solution of the sodium salt thereof, of less than 100 cps, thereby producing beads in which the rate of release of the basic medicament from the beads upon ingestion thereof is controlled.

2. Alginate gel beads produced according to the process of claim 1.

3. The alginate gel beads composition as set forth in claim 2, wherein the basic medicament is a beta-blocking agent.

4. The alginate gel beads composition as set forth in claim 3, wherein the beta-blocking agent is pindolol.

5. The alginate gel beads as set forth in claim 2, wherein the basic medicament is a calcium antagonistic agent.

6. The alginate gel beads composition as set forth in claim 5, wherein the calcium antagonistic agent is nifedipine.

7. The process as set forth in claim 1, wherein the solution contains 4% of the basic medicament suspended therein.

8. The process of claim 7, wherein the basic medicament is pindolol.

9. The process of claim 7, wherein the basic medicament is nifedipine.

10. The process as set forth in claim 1, wherein the suspension is added dropwise through a nozzle to the calcium chloride solution and then allowed to stand for about 72 hours.

11. The process as set forth in claim 1, wherein the viscosity (1% solution) is from 13.3 to 12.1.

12. The process of claim 1, wherein the basic medicament is pindolol or nifedipine and the solution contains 4% of sodium alginate, and wherein the suspension is added dropwise through a nozzle to the calcium chloride solution and then allowed to stand for about 72 hours.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,302,399

DATED : April 12, 1994

INVENTOR(S) : Masaki OTAGIRI et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page: Item (30) Foreign Application Priority Data:

Insert - - PCT/JP89/00255 March 09, 1989 - -

Signed and Sealed this

Ninth Day of August, 1994

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US006262034B1

(12) **United States Patent**
Mathiowitz et al.

(10) **Patent No.: US 6,262,034 B1**
(45) **Date of Patent: Jul. 17, 2001**

(54) **POLYMERIC GENE DELIVERY SYSTEM**

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(73) Assignee: **Neurotech S.A.**, Evry (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/978,522**

(22) Filed: **Nov. 25, 1997**

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(52) **U.S. Cl.** **514/44**; 435/69.1; 435/320.1; 435/91.4; 435/455; 424/468; 424/486; 424/484; 424/497

(58) **Field of Search** 435/455, 69.1, 435/320.1, 325, 91.4; 514/44; 536/23.1; 424/468, 486, 484, 497

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(57) **ABSTRACT**

A means for obtaining efficient introduction of exogenous genes into a patient, with long term expression of the gene, is disclosed. The gene, under control of an appropriate promoter for expression in a particular cell type, is encapsulated or dispersed with a biocompatible, preferably biodegradable polymeric matrix, where the gene is able to diffuse out of the matrix over an extended period of time, for example, a period of three to twelve months or longer. The matrix is preferably in the form of a microparticle such as a microsphere (where the gene is dispersed throughout a solid polymeric matrix) or microcapsule (gene is stored in the core of a polymeric shell), a film, an implant, or a coating on a device such as a stent. The size and composition of the polymeric device is selected to result in favorable release kinetics in tissue. The size is also selected according to the method of delivery which is to be used, typically injection or administration of a suspension by aerosol into the nasal and/or pulmonary areas. The matrix composition can be selected to not only have favorable degradation rates, but to be formed of a material which is bioadhesive, to further increase the effectiveness of transfer when administered to a mucosal surface.

14 Claims, No Drawings

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POLYMERIC GENE DELIVERY SYSTEM

This is a continuation, of application Ser. No. 08/467,811, filed Jun. 6, 1995, which is a division of application Ser. no. 08/213,668, filed Mar. 15, 1994.

BACKGROUND OF THE INVENTION

The present invention is generally in the area of drug delivery devices and is specifically in the area of polymeric drug delivery devices.

Gene therapy is generally defined as the introduction and expression of an exogenous gene in an animal to supplement or replace a defective or missing gene. Examples that have received a great deal of recent attention include the genes missing in cystic fibrosis and severe combined immunodeficiency. Although tremendous progress has been made in the area of gene therapy, obtaining long term expression of the desired proteins remains elusive.

In the majority of cases, a retroviral vector is used to introduce the gene to be expressed into appropriate cells. Gene transfer is most commonly achieved through a cell-mediated ex vivo therapy in which cells from the blood or tissue are genetically modified in the laboratory and subsequently returned to the patient. The clinical studies by Steven Rosenberg, et al., "Immunotherapy of patients with metastatic melanoma using tumor-infiltrating lymphocytes and IL-2", Preliminary report, *New England J. Med.,* 319 (1988) 1676–1680, using in vitro-activated LAK and TIL for tumor destruction illustrates this approach. In other cases, the vector carrying the gene to be expressed is introduced into the patient, for example, by inhalation into the lungs in the case of cystic fibrosis. Transfected cells have also been implanted, alone or encapsulated within a protective membrane that protects the cells from the inflammatory response of the body while at the same time allowing the gene product to diffuse out of the membrane. There have also been reports of the direct injection of an exogenous gene in combination with an appropriate promoter, into tissue, with some transient expression being noted.

Viral vectors have been widely used in gene transfer, due to the relatively high efficiency of transfection and potential long term effect through the actual integration into the host's genome. However, there are still concerns about the risks involved in the use of viruses. Activation of proto-oncogenes and reversion to wild-type viruses from replication incompetent viruses are some important potential hazards of viral delivery of genes.

Since the discovery that naked DNA is taken up by muscle cells and transiently expressed in vivo, and subsequent reports, by Wolff, Jon A et al., "Direct gene transfer into mouse muscle in vivo," *Science,* 247, 1465–1468, 1990; and Acsadi et al., "Human dystrophin expression in mdx mice after intramuscular injection of DNA constructs," *Nature,* 352, 815–818, 1991, there has been increasing interest in using non-viral vehicles for in vivo transfections.

Plasmid DNA, which can function episomally, has been used with liposome encapsulation, $CaPO_4$ precipitation and electroporation as an alternative to viral transfections. Recent clinical trials with liposome encapsulated DNA in treating melanoma illustrates this approach to gene therapy, as reported by Nabel, J. G., et al., "Direct gene transfer with DNA-liposome complexes in melanoma: Expression, biological activity and lack of toxicity in humans", *Proc. Nat. Acad. Sci. U.S.A.,* 90 (1993) 11307–11311. A foreign gene coding for HLA-B was introduced into subcutaneous sites of melanoma tumors. Expression of the new gene and the absence of an anti-DNA host response was confirmed. Wolff, Jon A, "Persistence of plasmid DNA and expression in rat brain cells in vivo," *Experimental Neurology,* 115, 400–413, 1992, also reported expression of plasmid DNA. Thus, direct gene transfer offers the potential to introduce DNA encoding proteins to treat human diseases.

The mechanisms for cellular uptake of exogenous DNA and subsequent expression are not clear but gene transfer with naked DNA is associated with several characteristics. Unlike in the case of oligonucleotides, which are typically a maximum of twenty to thirty nucleotides in length, genes encoding most molecules of therapeutic interest are quite large, and therefore considerably more difficult to introduce into cells other than through retroviral vector, or in vitro, by chemical manipulation, so that the efficiency of transfer is low. In most reported cases to date, only transient expression of up to a few weeks or months has been observed. Although low level expression and short term expression are two important drawbacks with direct DNA transfer, transfections with naked DNA have several advantages over viral transfers. Most importantly, concerns related to the immunogenicity and transforming capability of viruses are avoided. In addition, naked DNA is easy to produce in large quantities, is inexpensive, and can be injected at high concentration into localized tissue sites allowing gene expression in situ without extensive ex vivo therapy.

The following additional articles review the current state of gene therapy and the problems associated therewith: Blau, Helen M, "Muscling in on gene therapy," *Nature,* 364, 673–675, 1993; Cohen, Jon, "Naked DNA points way to vaccines," *Science,* 259, 1691–1692, 1993; Dagani, Ron, "Gene therapy advance, anti-HIV antibodies work inside cells," *C&EN,* 3–4, 1993; Felgner, Philip L, "Lipofectamine reagent: A new, higher efficiency polycationic liposome transfection reagent," *Focus/Gibco,* 15, 73–78, 1993; Liu, Margaret A et al., "Heterologous protection against influenza by injection of DNA encoding a viral protein," *Science,* 259, 1745–1749, 1993; Marx, Jean, "A first step toward gene therapy for hemophilia B," *Science,* 262, 29–30, 1993; Mulligan, Richard C, "The basic science of gene therapy," *Science,* 260, 926–931, 1993; Nicolau, Claude et al., "In vivo expression of rat insulin after intravenous administration of the liposome-entrapped gene for rat insulin I," *Proc. Natl. Acad. Sci. USA,* 80, 1068–1072, 1983; Partridge, Terence A, "Muscle transfection made easy," *Nature,* 352, 757–758, 1991; Wilson, James M, "Vehicles for gene therapy," *Nature,* 365, 691–692, 1993; Wivel, et al., "Germline gene modification and disease prevention: Some medical and ethical perspectives," *Science,* 262, 533–538, 1993; and Woo, Savio L C et al., "In vivo gene therapy of hemophilia B: sustained partial correction in Factor IX-deficient dogs," *Science,* 262, 117–119, 1993.

Gene therapy is one of the most promising areas of research today. It would therefore be extremely useful if one had an efficient way to introduce genes into cells which yielded long term expression.

It is therefore an object of the present invention to provide a means for efficient transfer of exogenous genes to cells in a patient.

It is a further object of the present invention to provide a means for long term expression of exogenous genes in patients.

It is a further object of the present invention to provide a means for increasing or decreasing the inflammatory response to implanted polymeric devices.

It is a still further object of the present invention to provide a method for immunization of individuals over a

more prolonged period of time than is achieved by a single or multiple immunization protocol.

It is another object of the present invention to provide a method for targeting of gene delivery either to tissue cells or to inflammatory type cells.

SUMMARY OF THE INVENTION

A means for obtaining efficient introduction of exogenous genes into a patient, with long term expression of the gene, is disclosed. The gene, under control of an appropriate promoter for expression in a particular cell type, is encapsulated or dispersed with a biocompatible, preferably biodegradable polymeric matrix, where the gene is able to diffuse out of the matrix over an extended period of time, for example, a period of three to twelve months or longer. The matrix is preferably in the form of a microparticle such as a microsphere where the gene is dispersed throughout a solid polymeric matrix) or microcapsule (gene is stored in the core of a polymeric shell), although other forms including films, coatings, gels, implants, and stents can also be used. The size and composition of the polymeric device is selected to result in favorable release kinetics in tissue. The size is also selected according to the method of delivery which is to be used, typically injection into a tissue or administration of a suspension by aerosol into the nasal and/or pulmonary areas. The matrix composition can be selected to not only have favorable degradation rates, but to be formed of a material which is bioadhesive, to further increase the effectiveness of transfer when administered to a mucosal surface, or selected not to degrade but to release by diffusion over an extended period.

Examples demonstrate the effectiveness of the system in animals.

DETAILED DESCRIPTION OF THE INVENTION

Gene transfer is achieved using a polymeric delivery system which releases entrapped genes, usually in combination with an appropriate promoter for expression of the gene, into surrounding tissue. Efficacy of transfer is achieved by: a) releasing the gene for prolonged period of time, b) minimizing diffusion of the gene out of the delivery system (due to its size) so that release is predominantly degradation dependent, and c) improving the transient time of expression and the low infection seen by direct gene therapy. In case of non-erodible polymers, the device is formulated so that the gene is released via diffusion. This is achieved by creating porous systems or adding soluble bulking agents that create pores as they leach out of the system.

The Polymeric Matrices

Selection of Polymer

Both non-biodegradable and biodegradable matrices can be used for delivery of genes, although biodegradable matrices are preferred. These may be natural or synthetic polymers, although synthetic polymers are preferred due to the better characterization of degradation and release profiles. The polymer is selected based on the period over which release is desired, generally in the range of at least three months to twelve months, although longer periods may be desirable. In some cases linear release may be most useful, although in others a pulse release or "bulk release" may provided more effective results. The polymer may be in the form of a hydrogel (typically in absorbing up to about 90% by weight of water), and can optionally be crosslinked with multivalent ions or polymers.

High molecular weight genes can be delivered partially by diffusion but mainly by degradation of the polymeric system. In this case, biodegradable polymers, bioerodible hydrogels, and protein delivery systems are particularly preferred. Representative synthetic polymers are: polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellullose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly (ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly (ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), poly(vinyl acetate, poly vinyl chloride, polystyrene and polyvinylpyrrolidone.

Examples of non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, polyamides, copolymers and mixtures thereof.

Examples of biodegradable polymers include synthetic polymers such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyurethanes, poly (butic acid), poly(valeric acid), and poly(lactide-co-caprolactone), and natural polymers such as alginate and other polysaccharides including dextran and cellulose, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water in vivo, by surface or bulk erosion.

Bioadhesive polymers of particular interest include bioerodible hydrogels described by H. S. Sawhney, C. P. Pathak and J. A. Hubell in *Macromolecules*, 1993, 26, 581–587, the teachings of which are incorporated herein, polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly (ethyl methacrylates), poly(butylmethacrylate), poly (isobutyl methacrylate), poly(hexylmethacrylate), poly (isodecyl methacrylate), poly(lauryl methacrylate), poly (phenyl methacrylate), poly(methyl acrylate), poly (isopropyl acrylate), poly(isobutyl acrylate), and poly (octadecyl acrylate).

Selection of Matrix Form and Size

In the preferred embodiment, the polymeric matrix is a microparticle between nanometers and one millimeter in diameter, more preferably between 0.5 and 100 microns for administration via injection or inhalation (aerosol).

The microparticles can be microspheres, where gene is dispersed within a solid polymeric matrix, or microcapsules, where the core is of a different material than the polymeric shell, and the gene is dispersed or suspended in the core,

which may be liquid or solid in nature. Unless specifically defined herein, microparticles, microspheres, and microcapsules are used interchangeably.

Alternatively, the polymer may be cast as a thin slab or film, ranging from nanometers to four centimeters, a powder produced by grinding or other standard techniques, or even a gel such as a hydrogel. The polymer can also be in the form of a coating or part of a stent or catheter, vascular graft, or other prosthetic device.

Methods for Making the Matrix

The matrices can be formed by solvent evaporation, spray drying, solvent extraction and other methods known to those skilled in the art.

Microsphere Preparation

Bioerodible microspheres can be prepared using any of the methods developed for making microspheres for drug delivery, for example, as described by Mathiowitz and Langer, *J. Controlled Release* 5,13–22 (1987); Mathiowitz, et al., *Reactive Polymers* 6, 275–283 (1987); and Mathiowitz, et al., *J. Appl. Polymer Sci.* 35, 755–774 (1988), the teachings of which are incorporated herein. The selection of the method depends on the polymer selection, the size, external morphology, and crystallinity that is desired, as described, for example, by Mathiowitz, et al., *Scanning Microscopy* 4,329–340 (1990); Mathiowitz, et al., *J. Appl. Polymer Sci.* 45, 125–134 (1992); and Benita, et al., *J. Pharm. Sci.* 73, 1721–1724 (1984), the teachings of which are incorporated herein.

In solvent evaporation, described for example, in Mathiowitz, et al., (1990), Benita, and U.S. Pat. No. 4,272,398 to Jaffe, the polymer is dissolved in a volatile organic solvent. The DNA, either in soluble form or dispersed as fine particles, is added to the polymer solution, and the mixture is suspended in an aqueous phase that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporates, leaving solid microspheres.

In general, the polymer can be dissolved in methylene chloride. Several different polymer concentrations can be used, for example, between 0.05 and 0.20 g/ml. After loading the solution with DNA, the solution is suspended in 200 ml of vigorously stirring distilled water containing 1% (w/v) poly(vinyl alcohol) (Sigma Chemical Co., St. Louis, Mo.). After four hours of stirring, the organic 'solvent will have evaporated from the polymer, and the resulting microspheres will be washed with water and dried overnight in a lyophilizer.

Microspheres with different sizes (1–1000 microns) and morphologies can be obtained by this method which is useful for relatively stable polymers such as polyesters and polystyrene. However, labile polymers such as polyanhydrides may degrade due to exposure to water. For these polymers, hot melt encapsulation and solvent removal may be preferred.

In hot melt encapsulation, the polymer is first melted and then mixed with the solid particles of DNA, preferably sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent such as silicon oil and, with continuous stirring, heated to 5° C. above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether to give a free-flowing powder. Microspheres with diameters between one and 1000 microns can be obtained with this method. The external surface of spheres prepared with this technique are usually smooth and dense. This procedure is useful with water labile polymers, but is limited to use with polymers with molecular weights between 1000 and 50000.

Solvent removal was primarily designed for use with polyanhydrides. In this method, the drug is dispersed or dissolved in a solution of a selected polymer in a volatile organic solvent like methylene chloride. The mixture is then suspended in oil, such as silicon oil, by stirring, to form an emulsion. Within 24 hours, the solvent diffuses into the oil phase and the emulsion droplets harden into solid polymer microspheres. Unlike solvent evaporation, this method can be used to make microspheres from polymers with high melting points and a wide range of molecular weights. Microspheres having a diameter between one and 300 microns can be obtained with this procedure. The external morphology of the spheres is highly dependent on the type of polymer used.

In spray drying, the polymer is dissolved in methylene chloride (0.04 g/ml). A known amount of active drug is suspended (if insoluble) or co-dissolved (if soluble) in the polymer solution. The solution or the dispersion is then spray-dried. Typical process parameters for a mini-spray drier are as follows: polymer concentration=0.04 g/ml, inlet temperature=24° C., outlet temperature=13 to 15° C., aspirator setting=15, pump setting=10 ml/min, spray flow=600 NLh^{-1}, and nozzle diameter=0.5 mm. Microspheres ranging in diameter between one and ten microns can be obtained with a morphology which depends on the selection of polymer.

Double walled microspheres can be prepared according to U.S. Pat. No. 4,861,627 to Mathiowitz.

Hydrogel microspheres made of gel-type polymers such as alginate or polyphosphazines or other dicarboxylic polymers can be prepared by dissolving the polymer in an aqueous solution, suspending the material to be incorporated into the mixture, and extruding the polymer mixture through a microdroplet forming device, equipped with a nitrogen gas jet. The resulting microspheres fall into a slowly stirring, ionic hardening bath, as described, for example, by Salib, et al., *Pharmazeutische Industrie* 40-11A, 1230 (1978), the teachings of which are incorporated herein. The advantage of this system is the ability to further modify the surface of the microspheres by coating them with polycationic polymers such as polylysine, after fabrication, for example, as described by Lim, et al., *J. Pharm. Sci.* 70, 351–354 (1981). For example, in the case of alginate, a hydrogel can be formed by ionically crosslinking the alginate with calcium ions, then crosslinking the outer surface of the microparticle with a polycation such as polylysine, after fabrication. The microsphere particle size will be controlled using various size extruders, polymer flow rates and gas flow rates.

Chitosan microspheres can be prepared by dissolving the polymer in acidic solution and crosslinking with tripolyphosphate. For example, carboxymethylcellulose (CMC) microsphere are prepared by dissolving the polymer in an acid solution and precipitating the microspheres with lead ions. Alginate/polyethylene imide (PEI) can be prepared to reduce the amount of carboxyl groups on the alginate microcapsules. Table 1 summarizes various hydrogels, concentrations, ionic baths, and stirring rates used to manufacture them.

TABLE 1

Preparation of Hydrogel Matrices

	Hydrogel	dissolving bath ionic bath stirring			
Hydrogel	concen.	pH	Temp ° C.	concen. (w/v)	rate
chitosan	1.0%	5.0	23° C.	3% tripoly-phosphate	170 rpm
alginate	2.0%	7.4	50° C.	1.3% calcium chloride	160 rpm
alginate/	2.0%/	7.4	50° C.	1.3% calcium	160 rpm

TABLE 1-continued

Preparation of Hydrogel Matrices					
	Hydrogel	dissolving bath ionic bath stirring			
Hydrogel	concen.	pH	Temp ° C.	concen. (w/v)	rate
PEI	6.0%	7.4	50° C.	chloride	
Carboxy methyl cellulose	2.0%	7.4	50° C.	10.0% lead nitrate	100 rpm

Other device forms

Other delivery systems including films, coatings, pellets, slabs, and devices can be fabricated using solvent or melt casting, and extrusion, as well as standard methods for making composites. The polymer can be produced by first mixing monomers and DNA as described by Sawhney, et al., and polymerizing the monomers with UV light. The polymerization can be carried out in vitro as well as in vivo. Thus, any biocompatible glue could be also used to incorporate the DNA.

Loading of Gene

The range of loading of the gene to be delivered is typically between about 0.01% and 90%, depending on the form and size of the gene to be delivered and the target tissue.

Selection of Genes to be Incorporated

Any genes that would be useful in replacing or supplementing a desired function, or achieving a desired effect such as the inhibition of tumor growth, could be introduced using the matrices described herein. As used herein, a "gene" is an isolated nucleic acid molecule of greater than thirty nucleotides, preferably one hundred nucleotides or more, in length.

Examples of genes which replace or supplement function include the genes encoding missing enzymes such as adenosine deaminase (ADA) which has been used in clinical trials to treat ADA deficiency and cofactors such as insulin and coagulation factor VIII.

Genes which effect regulation can also be administered, alone or in combination with a gene supplementing or replacing a specific function. For example, a gene encoding a protein which suppresses expression of a particular protein-encoding gene, or vice versa, which induces expresses of a protein-encoding gene, can be administered in the matrix..

Examples of genes which are useful in stimulation of the immune response include viral antigens and tumor antigens, as well as cytokines (tumor necrosis factor) and inducers of cytokines (endotoxin), and various pharmacological agents.

The chronic immune response to the polymeric matrix is mediated by the action of a variety of growth factors including epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFS), transforming growth factors (TGF-α and TGF-β, interleukin-1 (IL-1), and tumor necrosis factor (TNF). Inhibitors of these inflammatory mediators in combination with a gene to be delivered other than the immune inhibitor would be effective in decreasing the normal inflammatory response directed toward the polymeric matrix. By inhibiting the amount of encapsulation of the matrix, the effective release would be further extended. Examples of materials which could inhibit encapsulation include antisense mRNA to suppress fibrin or collagen formation, inhibitors of EGF, PDGF, FGFs, TGF-α, TGF-β, IL-1 and TNF and anti-inflammatory agents such as corticosteroids and cyclosporin.

Genes can be obtained using literature references or from commercial suppliers. They can be synthesized using solid phase synthesis if relatively small, or obtained in expression vectors, for example, as deposited with the American Type Culture Collection, Rockville, Md.

Selection of vectors to be introduced in combination with the gene.

As used herein, vectors are agents that transport the gene into the cell without degradation and include a promoter yielding expression of the gene in the cells into which it is delivered. Promoters can be general promoters, yielding expression in a variety of mammalian cells, or cell specific, or even nuclear versus cytoplasmic specific. These are known to those skilled in the art and can be constructed using standard molecular biology protocols. Although as demonstrated by the examples, the genes will diffuse out of the polymeric matrix into the surrounding cells where they are expressed, in a preferred embodiment, the genes are delivered in combination with a vector to further enhance uptake and expression. Vectors are divided into two classes:

a) Biological agents derived from viral, bacterial or other sources.

b) Chemical/ physical methods that increase the potential for gene uptake, directly introduce the gene into the nucleus or target the gene to a cell receptor.

Biological Vectors

Viral vectors have higher transaction (ability to introduce genes) abilities than do most chemical or physical methods to introduce genes into cells.

Retroviral vectors are the vectors most commonly used in clinical trials, since they carry a larger genetic payload than other viral vectors. However, they are not useful in non-proliferating cells.

Adenovirus vectors are relatively stable and easy to work with, have high titers, and can be delivered in aerosol formulation. However, many people may have pre-existing antibodies negating effectiveness and they are difficult to produce in quantity.

Pox viral vectors are large and have several sites for inserting genes, they are thermostable and can be stored at room temperature. However, they cannot be transmitted from host to host and there are some safety issues since they can enter other cells.

Plasmids are not integrated into the genome and their life span is from few weeks to several months, so they are typically very safe. However, they have lower expression levels than retroviruses and since cells have the ability to identify and eventually shut down foreign gene expression, the continuous release of DNA from the polymer to the target cells substantially increases the duration of functional expression while maintaining the benefit of the safety associated with non-viral transfections.

Chemical/physical vectors

Other methods to directly introduce genes into cells or exploit receptors on the surface of cells include the use of liposomes and lipids, ligands for specific cell surface receptors, cell receptors, and calcium phosphate and other chemical mediators, microinjections directly to single cells, electroporation and homologous recombination. The chemical/physical methods have a number of problems, however, and will typically not be used with the polymeric matrices described herein. For example, chemicals mediators are impractical for in vivo use: when calcium phosphate

is used there appears to be very low transduction rate, when sodium butyrate is used the inserted gene is highly unstable and when glycerol is used inserted gene is rapidly lost.

Pharmaceutical Compositions

The microparticles can be suspended in any appropriate pharmaceutical carrier, such as saline, for administration to a patient. In the most preferred embodiment, the microparticles will be stored in dry or lyophilized form until immediately before administration. They will then be suspended in sufficient solution for administration.

In some cases, it may be desirable to administer the microparticles in combination with an adjuvant to enhance the inflammatory response against the polymer and thereby increase the likelihood of phagocytosis by macrophages and other hematopoietic cells, with subsequent expression of the gene specifically within these cells, or, in the case where the microparticles contain an anti-cancer agent, to enhance the inflammatory reaction against the tumor cells in combination with the effect of the anti-cancer agent.

The polymeric microparticles can be administered by injection, infusion, implantation, orally (not preferred), or administration to a mucosal surface, for example, the nasal-pharyngeal region and/or lungs using an aerosol, or in a cream, ointment, spray, or other topical carrier, for example, to rectal or vaginal areas. The other devices are preferably administered by implantation in the area where release is desired.

The materials can also be incorporated into an appropriate vehicle for transdermal delivery as well as stents. Appropriate vehicles include ointments, lotions, patches, and other standard delivery means.

Targeting of cell populations through polymer material characteristics.

Studies with plasmid release using PLA/PCL biodegradable polymers indicate that the majority of transfected cells, assessed with the β-galactosidase reporter gene, are inflammatory cells involved in the "foreign body" response. In general, non-degrading polymers evoke a stronger inflammatory response when compared to non-biodegrading polymers. A strong foreign body response results in a thick layer of macrophages, fibroblasts, and lymphocytes around the implant. Because the polymer release device relies on diffusion for movement of its particles, a strong inflammatory response will limit the effective distance of diffusion. Accordingly, biodegrading polymers can be used to target inflammatory cells due to the inability of the plasmid DNA (pDNA) to migrate across the reactive tissue layer to the site specific tissue. A more biocompatible material which induces a weaker response from the host will result in a thinner layer of inflammatory cells, enabling the released pDNA to migrate across the inflammatory cells to the indigenous cells to be transfected.

Incorporation of Antiinflammatories and Immune Enhancers; Treatment of Cancers

In recent years, considerable attention has been focused on the use of gene therapy to treat various diseases including cancer. Generally, gene therapy for cancer therapeutics either targets the cells of the immune system to enhance their ability to kill malignant cells or directly targets the cancer cells to regulate their proliferation or enhance some cellular function which will result in a stronger activation of the immune response.

Most types of cancer are characterized by frequent relapses during the course of treatment and the continued non-specific and/or specific activation of the immune system resulting from gene therapy is crucial. Second, cell targeting is a major limitation of current vectors and implantation of a controlled release device directly inside a tumor where the DNA is released locally is one alternative to ex vivo therapy or the development of effective ligand specific vectors. As indicated by the prevalence of ex vivo therapy, targeting hematopoietic cells is especially difficult. The histological results from the implant site in the studies described in the examples below, reveal a substantial inflammatory response surrounding the intramuscular implant. The well known "foreign body" host response can be used to an advantage as this migration of lymphocytes and antigen presenting cells raises the possibility of directing the transfection to these specific cell populations.

Tumors elicit both the humoral and cell-mediated immune response, and lymphocytes, particularly cytotoxic T cells and NK cells, as well as macrophages, are known to play a crucial role in tumor elimination. Gene therapy for cancer treatment either targets these cells or the malignant cells themselves. An implant releasing naked DNA for long term functional gene transfer which can target inflammatory cells and/or tumor cells could significantly improve cancer therapy.

The approaches used include upregulation of class I MHC expression, transduction of antigen presenting cells with tumor-specific antigens, cytokine immunotherapy, transfection of tumor cells with tumor suppressor genes and anti-sense therapy.

The malignant transformation of cells is often characterized by a reduction of class I MHC expression leading to a severe depression of the CTL-mediated immune response. An increase in class I MHC expression on tumor cells could facilitate the activation of the immune system against these altered self-cells. Transfection of genes for cytokines such as tumor necrosis factor (TNF) into tumor cells or tumor suppressor genes such as p53 can be used to limit the ability of tumor cells to multiply. Anti-sense therapy targets cell proliferation or the production of necessary proteins such as tumor angiogenesis factor (TAF) by complementary RNA hybridization to block transcription of specific genes.

The immune system can be activated and induced to attack specific cells using cytokines such as Proleukin or monoclonal antibodies. For example, cancer cells proliferate in part due to a decreased immune response against the transformed cells. The matrices described herein provide a means to allow recognition and provocation of a response to cancer cells. For example, genes coding for antigens, such as the aberrant epithelial mucin of breast cancer, and monoclonal antibodies directed against tumor antigens have been shown to have potential in stimulating immune destruction of malignant cells. These genes, alone or in combination with monoclonal antibodies, can be delivered to the tumor sites in the polymeric matrices to achieve inhibition of the tumor cells.

Cancer cells can also be treated by introducing chemotherapy drug resistant genes into healthy cells to protect them against the toxicity of drug therapy, or by the insertion of appropriate vectors containing cytotoxic genes or blocking genes into a tumor mass to eliminate cancer cells. In a preferred embodiment, the immune system is specifically stimulated against antigens or proteins on the surface of the cancer cells.

These approaches can be used in vitro and in vivo. In vitro, the cells can be removed from a patient, the gene inserted into the cell and the cells reintroduced into the patient. In vivo, the gene can be directly introduced into the body either systematically or in localized sites.

Another approach is to use suicide genes that cause cell death when they are activated or when their product is

combined with a pharmaceutical. The primary limitation of the method is the fact that the gene should be targeted to the cancer cell and not to normal cell. Current approach to overcome the problem is direct injection of the vectors into a localized area where normal cells do not proliferate. This would be greatly facilitated using the polymeric devices described herein. The advantages of polymeric devices in this setting include continuous and protracted release of the incorporated pharmaceutical. This increases the liklihood that the intended purposes, for example, treatment of cancerous cells, will be achieved.

EXAMPLES

The method and materials of the present invention will be further understood by reference to the following non-limiting examples.

Example 1

Expression of Linear and Supercoiled Plasmid DNA Encapsulated in Polymeric Implants in Muscle Tissue of Rats

The study described in this example confirms the feasibility of in vivo transfections using biodegradable polyester blends to release linear or supercoiled plasmid DNA. Although only short term expression was studied in this study, polymer devices releasing drugs offer the potential for sustained long term delivery of naked DNA.

Marker genes are used to study the movement of engineered cells containing exogenous genes, as well as the vectors and genes introduced with the vectors, to insure that the genes remain where they are introduced. Almost all of the initial research into gene therapy is with marker genes. Preferred marker genes are those whose product is innocuous and which can be readily detected by simple laboratory tools. An appropriate marker gene is β-galactosidase (β-gal), since expression is readily detected by addition of X-gal, a substrate which yields a blue color when the active enzyme is present.

Encapsulation of linear and supercoiled β-gal coding DNA in a PLA blend

1 g PLA (300K) and 2 g polyactic acid (PLA) (2K) was dissolved in 10 ml of methylene chloride and 5 drops of sorbitan trioleate (SPAN™) 85. The mixture was divided into two aliquots of 5 ml and 100 ul of either circular or linear DNA (between 1 and 2 mg/ml diluted 1:5 in buffer) was introduced into the aliquots. Each mixture was mixed well and aliquoted into glass vials (1 ml/vial). Between 20 μg and 40 μg of β-gal plasmid DNA was encapsulated in each glass vial. The glass vials were left in the -refrigerator for four days to evaporate the methylene chloride and then lyophilized.

Implantation of DNA/PLA pellets

Each sample was first sterilized with ethanol for 5 min and then washed with PBS-penicillin/streptomycin for 5 min. Surgery was done on Sprague Dawley rats. Linear DNA was implanted into the left leg and supercoiled DNA implanted into the right. Implants were inserted into incised muscle—either in the vastus or the hamstring. The muscle was sutured back together and then the skin was sutured closed. Rats were sacrificed for analysis at two weeks.

Results

Rats were perfused with Phosphate Buffered Saline (PBS) with 2500 units of heparin followed by 3% paraformaldehyde and 0.2% glutaraldehyde in PBS. The tissue was post-fixed with 3% paraformaldehyde followed by 15% sucrose/PBS. Excised muscles were cut with a cryostat and stained with X-gal.

Histology of the implant sites revealed a substantial inflammatory response around the film at two weeks and two months. The bulk of the β-gal positive staining was localized to this area with few muscle cells exhibiting positive staining. The cells present around the implant probably consists of phagocytic cells, lymphocytes and fibroblasts. As expected, transfection was more efficient with supercoiled DNA.

Example 2

In vitro Transfection with pRSV β-gal

NIH3T3 fibroblasts were plated onto a 6 well tissue culture dish with 1 ml of D-MEM (10% Fetal calf serum with penicillin/streptomycin). 24 hours after plating, the cells were transfected with pRSV β-gal control plasmids as per Promega Profection Mammalian Transfection system.

Plate 1:	10 μl pRSV-Z (3.4 μg) Calcium Phosphate Precipitated
Plate 2:	30 μl pRSV-Z (10.2 μg) Calcium Phosphate Precipitated
Plate 3:	10 μl pRSV-Z (3.4 μg) Naked DNA
Plate 4:	30 μl pRSV-Z (10.2 μg) Naked DNA
Plate 5:	DNA/PLA
Plate 6:	Control

Plate 5 with the PLA pellet was placed into the well with 4 ml of media to counter the effect of the decrease in pH. After 24 hours, the DNA/PLA pellet was removed and the media left unchanged. At 48 hours, the cells were fixed and stained with X-Gal (1 ml/plate) overnight.

Results

The efficiency of transfection was very low. All plates except the control well had a handfull of blue staining cells. There was no observable differences in the number of blue cells among the 5 plates. It was interesting to note that the plate with the DNA/PLA had similar levels of staining as the other plates even after the fact that half the cells had died and detached due to the PLA degradation.

Example 3

Duration of Expression with pSV β-gal DNA Encapsulated into PLA Blends

In vitro release of plasmid DNA

pSV β-gal was amplified in HB101 and purified with Qiagen's Mega Prep. 500 μl of plasmid in Tris-EDTA buffer (67.5 μg) was lyophilized and resuspended into 100 μl of sterile dH_2O and incorporated into PLA. 0.05 g PLA (2K) and 0.05 g (300K) was dissolved in 1 ml of methylene chloride and 1 drop of SPAN™ 85. After the polymer was in solution, 100 μl of plasmid (67.5 μg) was added to the mixture and vortexed for 15 sec. The resulting film was left in a refrigerator overnight and subsequently lyophilized overnight.

This film was incubated with 1.0 ml of TE buffer at 37° C. under gentle agitation and sample supernatants tested at 24 hours and at 4 days for the presence of released DNA. DNA was assayed by agarose gel electrophoresis on the supernatants.

The results based on the gel of the supernatant after 24 hours of incubation show that a substantial amount of plasmid was released. After 4 days, the results indicate that there was a first phase of release due to the diffusion of plasmid molecules which are close to the surface of the device followed by a slower release at 4 days due to the low degradation rate of the polymer which was too low to be measured.

In vivo transfection levels

3 mg PLA (2K) and 1 mg PLA (1000K) were dissolved in methylene chloride (0.25 ml). 1 drop of SPAN™ 85 and 20

μl of plasmid (20 μg) was added to the solution and homogenized for 1 minute. This solution was air dried in a glass vial for 3 hours in a sterile hood. The brittle film was ground into fine granules and pressed into a pellet form. Three of these DNA containing pellets were made as well as three control pellets without DNA. All pellets were lyophilized overnight to extract residual solvents.

Three rats received DNA/PLA in their left hamstring and control/PLA in their right hamstring. Pellets were inserted into incised hamstrings and the muscles closed with 6-0 Vicryl. Three rats received an injection of pSV β-gal plasmids (20 μg in 100 μl of TE buffer) over a minute long period in their left leg and 100 μl of plain TE buffer in their right leg as controls. The site of injection was marked with suture.

Rat ID	Left	Right	Implant Duration
R112	DNA/PLA	Control/DNA	1 week
R110	DNA/PLA	Control/DNA	5 weeks
R111	DNA/PLA	Control/DNA	10 weeks
R115	DNA/buffer	Control/buffer	1 week
R114	DNA/buffer	Control/buffer	5 weeks

Rats were perfused with PBS/heparin, followed by 4% paraformaldehyde, and post-fixed in 4% paraformaldehyde followed by 15% and 25% sucrose/PBS. Excised muscles were cut with a cryostat and stained with X-Gal.

Results

In vitro release studies indicate that plasmid DNA can be incorporated into polymers without degradation through manufacturing processes and released in functional form for possible uptake by surrounding cells.

In vivo studies reveal that with a 20 μg loading of DNA into the polymer, there is substantial transfection of inflammatory cells at 1 and 5 weeks as confirmed by X-gal staining and immunoblotting. At 10 weeks, there was no difference in staining intensity between the control PLA and DNA/PLA. This is believed to be due to the result of the low loading (20 μg) of the polymer such that after one week the release rate was below half maximal levels. Investigators using direct injection use doses in the 100 μg range to see their effects. A higher initial loading, which will lead to continued release of higher amounts of DNA from polymers, should prolong transfection durations. Rats injected with 20 μg of DNA in solution showed no transfection at 1 and 5 weeks.

Example 4

Comparison of Plasmid DNA Release From Biodegradable and Non-degrading Polymers

Release of plasmids from biodegradable and non-degradable polymer was compared to test the feasibility of targeting either inflammatory cells or tissue specific cells by selection of polymer material. Plasmid DNA was incorporated into a non-degradable elastomer, ethylene vinyl acetate copolymer (EVAc) and implanted into the same site in different animals as PLA/PCL implants. EVAc is a very biocompatible polymer which can be manufactured into a microporous structure through which DNA can diffuse into the surrounding tissue.

Encapsulation of pRSV β-gal into Polymers.

pRSV β-gal in HB101 was purchased from the ATCC (American Type Culture Collection, Rockville, Md.). The plasmids were grown and purified with Promega's Maxi Prep. 1 ml of a 0.1% solution of ELVAX40 (Dupont) in methylene chloride was vortexed with 645.2 μl of pRSV β-gal (200 μg), frozen in liquid nitrogen and lyophilized. The resulting mixture was extruded at 55° C. into a rod shaped form.

PLA (2K) and polycaprolactone (PCL) (112K) were dissolved in methylene chloride in a 3:1 ratio and 80 mg of the polymer vortexed with 322.6 μl of pRSV β-gal (100 μg). The mixture was left in the refrigerator for 2 days and lyophilized.

Implantation of the Polymers.

The EVAc/DNA and PLA/DNA were implanted into rat hamstrings along with their control on opposite sides and sacrificed at 2 weeks.

Results.

Histological staining with X-gal reveals positive staining of muscle cells as well as inflammatory cells in close proximity to the EVAc polymeric implant at two weeks post-implantation. In comparison, the PLA/PCL implant reveals positive staining of mostly inflammatory cells only, in accordance with the earlier data regarding biodegradable polymers.

Thus the selection of a biodegradable or non-degradable polymer implant can be used to target delivery to inflammatory cells or tissue cells (for example, muscle). Comparison of PLA/PCL and the EVAc implants illustrates the different transfected cell populations. Specifically, the PLA/PCL implant results in almost exclusive transfection of inflammatory cells while the EVAc implant results in a large number of transfected muscle cells.

Modifications and variations of the method and compositions of the present invention will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the following claims.

We claim:

1. A method of delivering naked DNA to a tissue site of a mammalian subject, said method comprising implanting directly, into said tissue site in said subject, a composition comprising:

(a) a preparation of microparticles between 1 and 300 μm in diameter, each of which preparation of microparticles comprises a synthetic, biocompatible, non-biodegradable polymeric matrix; and

(b) an effective amount of naked DNA contained within said matrix, wherein said amount of naked DNA is greater than 20 μg, and wherein the DNA contains a gene operably linked to a promoter, the nucleotide sequence of said gene being greater than thirty nucleotides in length;

wherein said DNA is released or diffused from said matrix after implantation over a period of at least three months.

2. The method of claim 1, wherein approximately 0.1–90% by weight of naked DNA is loaded into the polymeric matrix.

3. The method of claim 1, wherein the microparticles are approximately between 1 and 100 μm in diameter.

4. The method of claim 1, wherein the microparticles are approximately between 1 and 10 μm in diameter.

5. The method of claim 1, wherein the naked DNA is greater than one hundred nucleotides in length.

6. The method of claim 1, wherein the naked DNA comprises supercoiled DNA.

7. A composition for delivery of naked DNA into a cell comprising:

(a) a preparation of microparticles between approximately 1 and 300 μm in diameter, each of which preparation of microparticles comprises a synthetic polymeric matrix; and

(b) an effective amount of naked DNA contained within said matrix, wherein said amount of naked DNA is greater than 20 μg, and wherein the DNA contains a gene operably linked to a promoter, the nucleotide sequence of said gene being greater than thirty nucleotides in length;

wherein said DNA is released, or diffuses from said matrix after implantation over a period of at least three months.

8. The composition of claim **7**, wherein the microparticles are between approximately 1 and 100 μm in diameter.

9. The composition of claim **7**, wherein the microparticles are between approximately 1 and 10 μm in diameter.

10. The composition of claim **7**, wherein the polymeric matrix is biodegradable.

11. The composition of claim **7**, wherein the polymeric matrix is non-biodegradable.

12. The composition of claim **7**, wherein approximately 0.1–90% by weight of the naked DNA is loaded into the polymeric matrix.

13. The composition of claim **7**, wherein the naked DNA is greater than one hundred nucleotides in length.

14. The composition of claim **7**, wherein the naked DNA comprises supercoiled DNA.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,262,034 B1
DATED : July 17, 2001
INVENTOR(S) : Edith Mathiowitz et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [73], Assignee: should read as follows:
-- [73] Assignee: **Brown University Research Foundation,**
Providence, RI (US) --.

Signed and Sealed this

Seventh Day of May, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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This certificate supersedes the Certificate of Correction issued May 7, 2002, since this patent number did not appear on the Certificates of Correction listing for May 7, 2002.

Signed and Sealed this

Second Day of July, 2002

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Director of the United States Patent and Trademark Office

US006258055B1

(12) **United States Patent**
McCrory et al.

(10) **Patent No.: US 6,258,055 B1**
(45) **Date of Patent: Jul. 10, 2001**

(54) **SYSTEM FOR IMPLANTING A CROSS-LINKED POLYSACCHARIDE FIBER AND METHODS OF FORMING AND INSERTING THE FIBER**

(75) Inventors: **Jennifer McCrory**, Sunnyvale, CA (US); **Patrik Lüscher**, Pfäffikon (CH); **Kalpana Kamath**, Natick; **Ronald Sahatjian**, Lexington, both of MA (US)

(73) Assignee: **Boston Scientific Corporation**, Natick, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/617,132**

(22) Filed: **Jul. 14, 2000**

Related U.S. Application Data

(62) Continuation of application No. 08/919,107, filed on Aug. 28, 1997, now Pat. No. 6,139,520, which is a continuation-in-part of application No. 08/776,943, filed as application No. PCT/CH95/00184 on Aug. 16, 1995.

(30) **Foreign Application Priority Data**

Aug. 17, 1994 (CH) 2533/94

(51) **Int. Cl.**[7] **A61M 31/00**

(52) **U.S. Cl.** **604/60**; 604/57; 604/82; 606/151; 606/167

(58) **Field of Search** 606/1, 159, 167, 606/170, 171, 213, 151; 604/19, 22, 11, 13–18, 506, 518, 57, 59, 60, 62, 82, 85, 365; 602/41, 44, 45, 49, 50; 536/54, 3, 106

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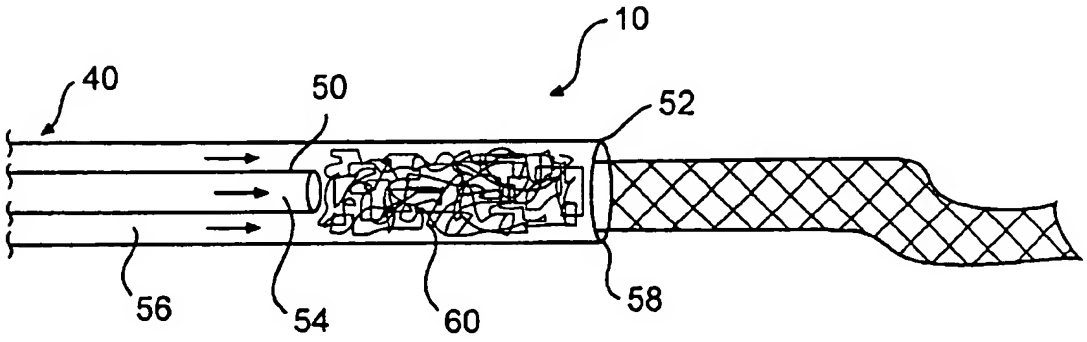
Primary Examiner—Glenn K. Dawson
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

(57) **ABSTRACT**

Systems and methods are disclosed for implanting and forming both a polysaccharide fiber and an implant formed of the fiber. In one system, a liquid including polysaccharide and a liquid including a cross linking agent are mixed in a cannula to form a cross linked polysaccharide fiber in the cannula. In another system, a carrier fluid delivers a previously manufactured fiber through a cannula. A cutter is optionally provided on the cannula to sever the fiber after a sufficient length of fiber is implanted. The disclosed methods include a method of forming a polysaccharide fiber in the cannula while the cannula is inserted in a body, and a method of making a cross linked polysaccharide fiber for loading in a delivery system.

15 Claims, 5 Drawing Sheets



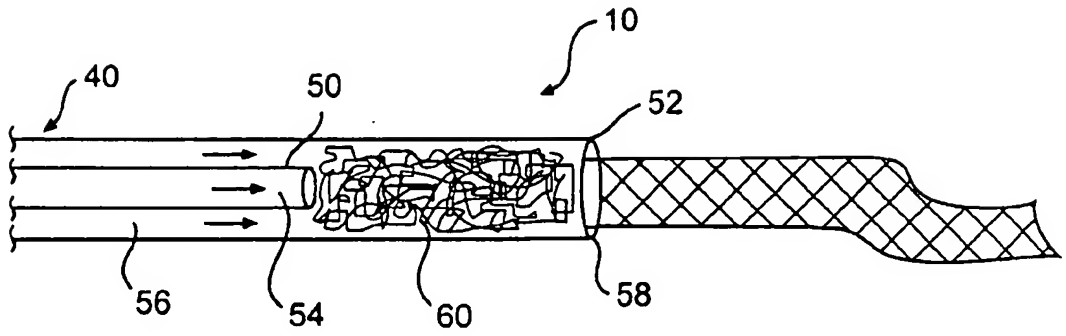

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FIG. 1

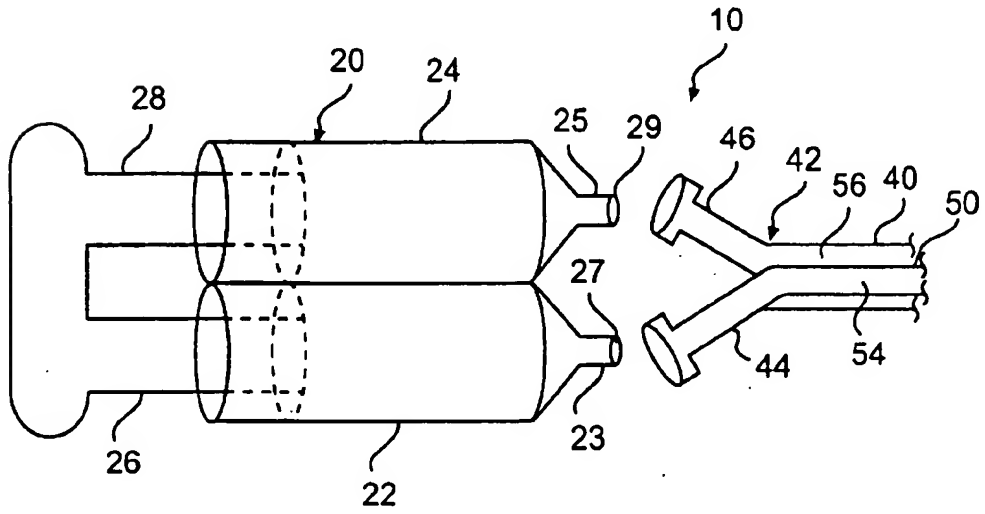
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FIG. 2

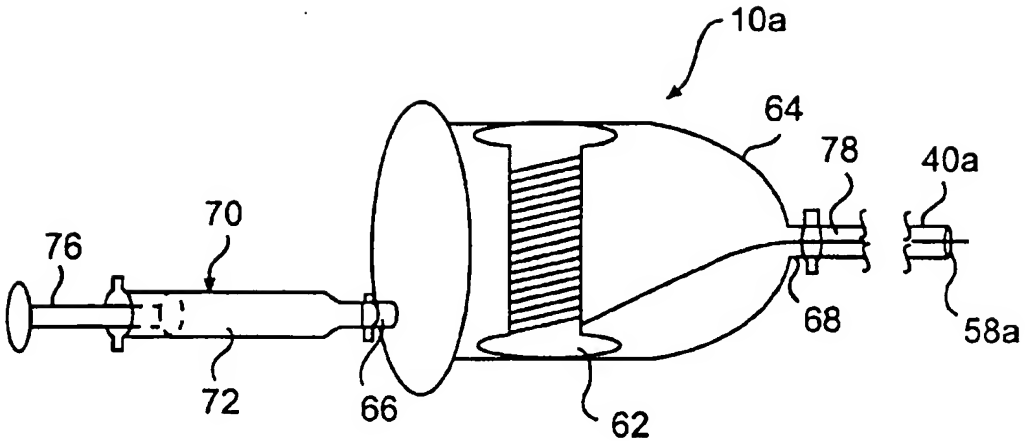

FIG. 3

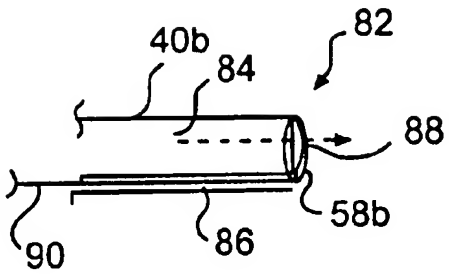

FIG. 4

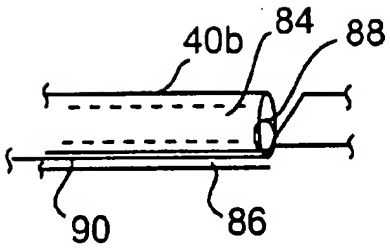

FIG. 5A

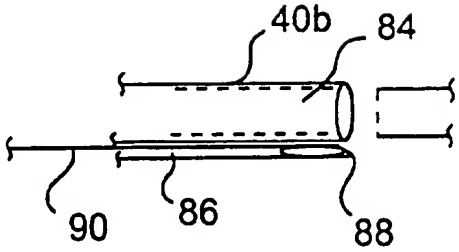

FIG. 5B

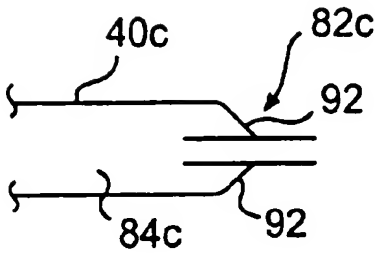

FIG. 6

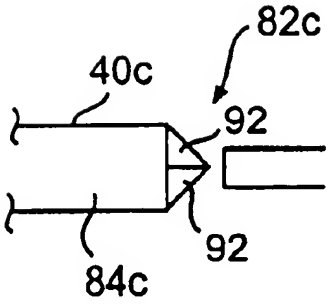

FIG. 7

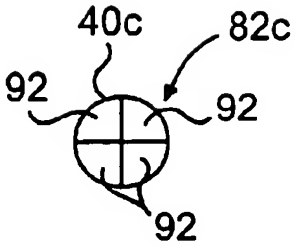

FIG. 8

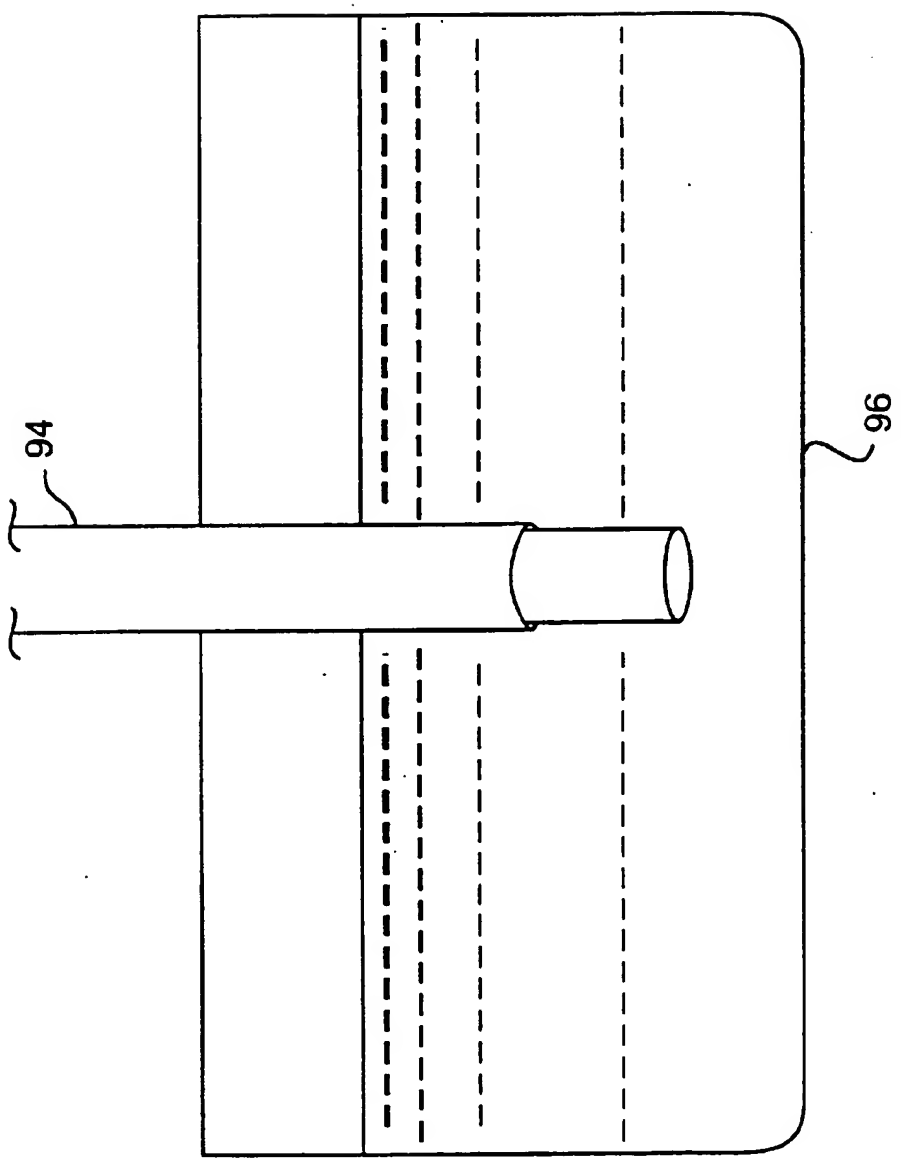

FIG. 9

SYSTEM FOR IMPLANTING A CROSS-LINKED POLYSACCHARIDE FIBER AND METHODS OF FORMING AND INSERTING THE FIBER

This is a continuation of U.S. application Ser. No. 08/919,107, filed Aug. 28, 1997, now U.S. Pat. No. 6,134,520, which is a continuation-in-part of U.S. application Ser. No. 08/776,943, filed Apr. 21, 1997 (pending), which is an application under 35 U.S.C. § 371 of PCT/CH95/00184, filed Aug. 16, 1995, the entire disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to implant systems and methods of forming and inserting a fiber. More particularly, the present invention relates to systems and methods for mixing a liquid including polysaccharide and a liquid including a cross linking agent to form a cross linked polysaccharide fiber.

2. Description of Related Art

Alginate is a polysaccharide material derived from brown seaweed. Although the predominate use of alginates is as a food additive to thicken and stabilize solutions, they are also used in various medical applications. Alginate can be easily cross linked into biocompatible hydrogels used as a cell immobilization matrix for various biotechnology applications. In addition, this substance can be used as a biodegradable gel/film coating in pharmaceutical applications. Alginate is also used to make wound dressings and pads capable of absorbing wound exudate and providing a moisture permeable wound covering.

By coming in contact with different ionic substances having certain affinities, alginate and other polysaccharides can exist in either a liquid or solid phase. In addition, alginates and other polysaccharides are capable of being reversibly cross linked so that they can either degrade or cross link on demand. The present invention relies on the ability of these materials to cross link on demand.

The inventors have discovered that alginate and other polysaccharides are particularly useful materials for forming a biocompatible implant. In addition, the inventors have discovered that implants formed of these materials are particularly useful in the treatment of intracranial aneurysms.

Intracranial aneurysms are extremely difficult to treat because they are often formed in remote cerebral blood vessels, which are very difficult to access. If left untreated, hemodynamic forces of normal pulsatile blood flow can rupture fragile tissue in the area of the aneurysm causing a stroke. In one type of treatment, coils are implanted in the body of a patient in an attempt to occlude blood flow to the aneurysm. However, this procedure is time consuming because it often requires bi-plane X-rays after placement of each coil. In addition, a procedurist normally needs to determine and select the proper size for the coils prior to implantation. Also, coils can compact over time because they fill approximately 40% of the aneurysm volume only.

In light of the foregoing, there is a need in the art for an improved implant and systems and methods for forming and implanting this implant.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to systems and methods that substantially obviate one or more of the limitations of the related art. To achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described herein, the invention includes an implant system including a first reservoir containing a first liquid including polysaccharide, and a second reservoir containing a second liquid including an ionic cross linking agent. The system also includes a cannula including a first lumen in fluid communication with the first liquid in the first reservoir, a second lumen in fluid communication with the second liquid in the second reservoir, a distal end portion wherein the first and second lumens fluidly communicate with one another to mix the first and second liquids and thereby form a cross linked elongate fiber, and an opening in the distal end portion allowing passage of the cross linked fiber therethrough.

In another aspect, the present invention includes a method of forming an implant in a body. The method includes introducing a cannula into the body, the cannula including a first lumen, a second lumen, and an opening in a distal end portion of the cannula. The first liquid is passed through the first lumen, and the second liquid is passed through the second lumen. The method also includes mixing the first and second liquids in the cannula to form a flexible cross linked fiber, moving the fiber through the opening in the cannula, and contacting the fiber against body tissue to allow the fiber to bend and to form the implant in the body.

In another aspect, the invention includes a method of forming a fiber for an implant. The method comprises passing the first liquid through a tubular member placed in a reservoir containing the second liquid, and flowing the first liquid into the second liquid via an opening in a distal end portion of the tubular member. The polysaccharide and the ions of the cross linking agent then cross link to form an elongate fiber.

In an aspect of the invention, the polysaccharide of the first liquid includes alginate, and the cross linking agent of the second liquid includes calcium.

In an additional aspect, the system for inserting the fiber includes a spool having fiber wound thereon, a chamber containing the spool, the chamber having an interior, a first opening, and a second opening, and a syringe including a barrel in fluid communication with the first opening and a plunger movable in the barrel, movement of the plunger in the barrel pressurizing the interior of the chamber to deliver the fiber through the second opening.

In a further aspect, a cutter is provided on the cannula to sever a portion of the fiber passing through the lumen and opening of the cannula.

It is to be understood that both the foregoing general description and the following detailed description are exemplary, and are intended to provide further explanation of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute a part of this specification. The drawings illustrate embodiments of the invention and, together with the description, serve to explain the principles of the invention. In the drawings,

FIG. 1 is a view of a distal end portion of a cannula of a first embodiment of the invention;

FIG. 2 is a view of a proximal end portion of the cannula of FIG. 1 and a dual barrel syringe for coupling to the cannula;

FIG. 3 is a view of a chamber, syringe, and cannula of a second embodiment of the invention;

FIG. 4 is a view of a cutter for the cannulas shown in FIGS. 1 and 2 and FIG. 3;

FIGS. 5*a* and 5*b* are views showing how the cutter of FIG. 4 severs a fiber;

FIG. 6 is a view of an alternate embodiment of a cutter for the cannulas shown in FIGS. 1 and 2 and 3;

FIG. 7 is a view of the cutter of FIG. 6 after the cutter severs a fiber;

FIG. 8 is a distal end view of the cutter of FIG. 7; and

FIG. 9 is a view of a tubular member and reservoir used to form a fiber contained in the chamber shown in FIG. 3.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference will now be made in detail to the present preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings. Wherever possible, the same reference numbers are used in the drawings and the description to refer to the same or like parts, and the same reference numerals with alphabetical suffixes are used to refer to similar parts.

In accordance with the invention, there is provided an implant system including first and second reservoirs and a cannula having first and second lumens. FIGS. 1 and 2 respectively show distal and proximal end portions of a first embodiment of a system **10** in accordance with the present invention. As shown in FIG. 2, the system **10** includes a syringe **20** and a cannula **40** capable of being coupled together to introduce substances from the syringe **20** into the cannula **40**.

The syringe **20** includes a first barrel **22** having a tip **23** formed with a discharge opening **27** and a second barrel **24** having a tip **25** formed with a discharge opening **29**. The first and second barrels **22** and **24** respectively form a first reservoir containing a first liquid and a second reservoir containing a second liquid.

Preferably, the first liquid includes a polysaccharide, such as alginate (i.e., sodium alginate, potassium alginate, barium alginate, magnesium alginate, or strontium alginate, or mixtures thereof), chitosan, or a carboxylic acid containing polysaccharide. The second liquid preferably includes an ionic cross linking agent. When the polysaccharide of the first liquid is alginate, the ionic cross linking agent of the second liquid includes polyvalent cations, such as divalent cations. When the first liquid includes chitosan, the second liquid includes a compatible ionic cross linking agent, such as polyacrylic acid, heparin, or sodium carboxymethyl cellulose. For example, the first liquid is preferably a liquid including sodium alginate, and the second liquid is preferably a liquid solution including calcium, such as a liquid solution including calcium chloride, calcium gluconate, or calcium sulfate, or mixtures thereof.

As described below, the polysaccharide and the cross linking agent form a cross linked polysaccharide fiber when they are mixed in the cannula **40**. The first and second barrels **22** and **24** are preferably separate from one another to prevent this cross linking from taking place in the syringe **20**.

The syringe **20** also includes a first plunger **26** movable in the first barrel **22** and a second plunger **28** movable in the second barrel **24**. Preferably, the first and second plungers **26** and **28** are coupled together so that they move together in the respective barrels **22** and **24** to eject the first and second liquids simultaneously from the discharge openings **27** and **29**. As compared to separate plunger arrangements, the coupled first and second plungers **26** and **28** make it easier for a user to eject the first and second liquids at constant rates to form a more consistent cross linked fiber.

As shown in FIG. 2, the proximal end portion of the cannula **40** includes an adapter **42** having first and second branches **44** and **46** capable of being coupled directly to the respective tips **23** and **25**. Although the first and second branches **44** and **46** are preferably coupled directly to the tips **23** and **25**, other coupling arrangements are possible. For example, separate lengths of flexible tubing could be provided to couple the tips **23** and **25** and the branches **44** and **46** fluidly together. In addition, the first and second branches **44** and **46** could be located at different locations on the cannula **40** without both being on the same adapter **42**.

Preferably, the cannula **40** is a catheter having sufficient flexibility to allow for insertion into predetermined areas in a body. For example, the cannula **40** could be a flexible catheter, such as a micro catheter sufficiently flexible to be inserted into the cranial area to treat an aneurysm. In addition, the cannula **40** could be an endoscopic device, needle, or any other type of medical device having a generally tubular shape. Although the cannula **40** is preferably formed of a polymer, other materials, such as metal, can be used. To allow for imaging in the body, the cannula **40** preferably includes a portion or portions including radiopaque material.

As shown in FIG. 1, the cannula **40** includes a first tubular portion **50**, a second tubular portion **52**, and an opening **58** formed in the distal end of the cannula **40**. The first tubular portion **50** is positioned coaxially within the second tubular portion **52** to form a first lumen **54** in the first tubular portion **50**, and a second lumen **56** between an outer surface of the first tubular portion **50** and an inner surface of the second tubular portion **52**. When the syringe **20** shown in FIG. 2 is coupled to the adapter **42** on the cannula **40**, the first lumen **54** is placed in fluid communication with the first liquid in the first barrel **22**, and the second lumen **56** is placed in fluid communication with the second liquid in the second barrel **24**.

The first lumen **54** extends from the first branch **44** shown in FIG. 2 to its distal end shown in FIG. 1, and the second lumen **56** extends from the second branch **46** shown in FIG. 2 to its distal end shown in FIG. 1. Although the first and second lumens **54** and **56** are coaxially arranged and formed by the first and second tubular portions **50** and **52**, other configurations are possible. For example, the first and second lumens could be parallel lumens having independent axes and feeding into a single lumen segment (mixing chamber) at the distal tip portion of the catheter.

The distal end of the second tubular portion **52** extends further in the distal direction than the distal end of the first tubular portion **50**. This staggered end relationship of the tubular portions **50** and **52** forms a mixing chamber **60** in the distal end portion of the cannula **40** between the first tubular portion **50** and the opening **58**. The first and second lumens **54** and **56** communicate with one another in the mixing chamber **60**. As the first and second liquids flow from the first and second lumens **54** and **56** to the mixing chamber **60**, these liquids mix and form the cross linked polysaccharide fiber in the mixing chamber **60**. The resulting fiber is flexible and has a diameter substantially the same as that of the inner surface of the second tubular portion **52**. After the fiber is formed, it is extruded from the cannula **40** via the opening **58**.

Preferably, the first liquid contained in the first barrel **22** of the syringe **20** is a solution including a polysaccharide, such as sodium alginate , and the second liquid contained in the second barrel **24** of the syringe **20** is a solution including an ionic cross linking agent, such as calcium (i.e. calcium chloride) or some other cross linking agent having divalent ions. For example, when sodium alginate and calcium chloride combine in the mixing chamber **60**, the divalent cations (calcium ions) replace the sodium ions to form a cross linked, hydrogel, alginate fiber. Because the resulting cross linked alginate fiber is a hydrogel, it is possible to capture certain contrast substances into the gel to make the fiber visible in MRI, CT, and fluoroscopy.

For example, radiopaque substances, such as tantalum, tungsten, barium sulfate, and/or titanium dioxide can be added to the first liquid and/ or the second liquid to make the formed fiber radiopaque. In addition, barium, which is a divalent cation, can be used to cross link with the polysaccharide and make it radiopaque. Certain solutions of iodine and/or gadolinium can also be solubilized in the liquid including polysaccharide prior to cross linking and may remain trapped within the gel after cross linking, making it visible in certain imaging modalities. In particular, gadopentetate dimeglumine and/or iothalamate meglumine, which are water soluble salts used as contrast agents, can be combined with the polysaccharide to produce a gel visible in both MRI and x-ray modalities (fluoroscopy, CT, DSA).

Certain drugs can also be added to the first and second liquids prior to forming the fiber. These drugs can also be captured in the cross linked fiber as it forms in the mixing chamber **60**. After implantation of the fiber in the body, the drugs are preferably released over time to provide particular treatments. For example, alcohol could be added to the first and/or second liquid to provide a fiber capable of treating an arteriovenous malformation (AVM)—an abnormal network of vessel connections between an artery and vein. In addition, thrombogenic substances could be added to one of the liquids to form a fiber capable of inducing thrombosis in an aneurysm cavity.

A precipitating material can also be added to the first liquid and/or the second liquid prior to forming the fiber. The precipitating material precipitates and forms a matrix as the fiber is formed. This matrix preferably holds portions of the fiber together to stabilize the implant structure formed by the fiber and to prevent fiber migration in the body. For example, polyvinyl alcohol, sucrose acetate, or cellulose acetate could be added to the first liquid and/or the second liquid to form the matrix. The matrix may be desired when using the fiber to pack a cavity, such as an aneurysm sac.

Alternatively, an adhesive material, such as cyanoacrylate adhesive, could be added to the first liquid and/or second liquid so that portions of the fiber adhere to one another after implant formation. This adherence stabilizes the implant and prevents fiber migration, especially when packing a cavity.

When the first liquid includes alginate, the first liquid and/or the second liquid also may include a different polysaccharide, such as chitosan. Chitosan forms an electrostatic interaction with alginate. When a cross linked alginate fiber is formed, chitosan and alginate form a polymer entanglement to provide structural integrity.

FIG. **3** shows a system **10***a* for implanting a fiber in the body in accordance with a second embodiment of the invention. The system **10***a* includes a spool **62** having fiber wound thereon and a chamber **64** containing the spool **62**. Preferably, the fiber on the spool **62** is a cross linked polysaccharide fiber, such as a cross linked alginate fiber, similar or identical to the fiber formed by the system **10** described above. The spool **62** is mounted in an interior of the chamber **64** so that the spool **62** is capable of rotating about its axis to unwind the fiber from the spool **62**.

The chamber **64** includes a first adapter **66** and a second adapter **68** having respective openings in fluid communication with the interior of the chamber **64**. As shown in FIG. **3**, the system **10***a* also includes a syringe **70** having a barrel **72** coupled to the first adapter **66**, and a cannula **40***a* having a proximal end hub coupled to the second adapter **68**. The syringe barrel **72** and interior of the chamber **64** contain a carrier fluid, such as saline solution, for conveying the fiber. A movable plunger **76** in the barrel **72** of the syringe **70** ejects the carrier fluid from the barrel **72** to the chamber **64**.

When the plunger **76** of the syringe **70** forces carrier fluid into the chamber **64**, the carrier fluid in the chamber **64** becomes pressurized and flows through the second adapter **68** and cannula **40***a*. As the carrier fluid flows from the chamber **64**, it conveys the fiber along with it. The fiber moves because the pressure of the carrier fluid in the chamber **64** is greater than the pressure in a distal end portion of cannula **40***a* and because friction exists between the carrier fluid and the fiber. Initially, the carrier fluid conveys the free end of the fiber through the second adapter **68** and cannula **40***a*. Then, the carrier fluid continues the conveyance of the fiber while the spool **62** rotates to unwind the fiber.

The cannula **40***a* includes at least one lumen **78** and an opening **58***a* in a distal end portion for allowing passage of the fiber therethrough. Because the cannula **40***a* only requires a single lumen, it can be small enough and flexible enough to reach distal cerebral vasculature. Although the cannula **40***a* preferably includes a single lumen rather than a plurality of lumens, it is otherwise constructed like the cannula **40** described in connection with the first embodiment. In other words, the cannula **40***a* can be a flexible catheter, micro catheter, endoscopic device, needle, or any other medical device having a generally tubular shaped portion.

Placing the spool **62** in the chamber **64** rather than in the barrel **72** allows for the use of both a smaller syringe and a larger compartment for holding the fiber, as compared to an arrangement wherein the spool is placed in the syringe barrel itself.

FIG. **4** shows an embodiment of the invention including a cutter **82** for severing the fiber. The cutter **82** is on a distal end portion of a cannula **40***b* including a primary lumen **84**, an auxiliary lumen **86**, and a distal opening **58***b*. With the exception of the auxiliary lumen **86**, the cannula **40***b* is preferably constructed like the cannula **40** shown in FIGS. **1** and **2**, the cannula **40***a* shown in FIG. **3**, or one of the cannulas disclosed in above-mentioned U.S. patent application Ser. No. 08/776,943, the disclosure of which has been incorporated by reference.

The cutter **82** is preferably a strand of wire having a loop shaped portion **88** and a substantially straight actuator portion **90** extending from the loop shaped portion **88**. The loop shaped portion **88** is positioned in the distal end portion of the cannula **40***b* along an inner surface of the lumen **84** so that the loop shaped portion **88** surrounds the fiber when the fiber passes through the lumen **84** and the opening **58***b*. The actuator portion **90** extends through the auxiliary lumen **86** to a proximal end portion of the cannula **40***b*. Alternatively, the actuator portion **90** extends through the primary lumen **84** or on the outside of the cannula **40***b* when the cannula does not have an auxiliary lumen.

FIGS. 5*a* and 5*b* show how the cutter 82 severs the fiber after a desired length of fiber has passed through the opening 58*b*. As shown in FIG. 5*a*, when the actuator 90 is moved in the proximal direction with respect to the cannula 40*b*, the loop shaped portion 88 passes across the lumen 84 and through the fiber to begin severing the fiber. Continued pulling of the actuator 88, completely severs the fiber, as shown in FIG. 5*b*, and places the loop shaped portion in the auxiliary lumen 86.

FIGS. 6, 7, and 8 show an alternate embodiment of a cutter 82*c* for severing the fiber. The cutter 82*c* is mounted on a cannula 40*c* constructed like the cannula 40 shown in FIGS. 1 and 2, the cannula 40*a* shown in FIG. 3, or one of the cannulas disclosed in above-mentioned U.S. patent application Ser. No. 08/776,943. The cannula 40*c* includes a lumen 84*c* allowing for passage of the fiber therethrough.

As shown in the distal end view of FIG. 8, the cutter 82*c* includes a plurality of resilient flaps or leaflets 92 biased toward one another to form a compliant slit valve. The leaflets 92 move away from one another in response to movement of the fiber against an inner surface of the leaflets 92 and increased fluid pressure in the lumen 84*c* generated by the syringe 20 shown in FIG. 2 or the syringe 70 shown in FIG. 3. As shown in FIG. 6, sufficient pressure of the fiber and fluid in the lumen 84*c* forces the leaflets 92 away from one another to create an opening having a size sufficient to allow for passage of the fiber from the distal end portion of the cannula 40*c*. When this pressure is reduced, the leaflets 92 resiliently close on the fiber to sever or pinch off the fiber, as shown in FIG. 7.

In an alternate embodiment, the adapter 42, shown in FIG. 2, is configured to allow an operator to move the first tubular portion 50, shown in FIGS. 1 and 2, axially in the second tubular portion 52. With such an arrangement, the first tubular portion 50 may be moved axially toward the distal opening 58 to push the formed fiber from the mixing chamber 60 and thereby separate the fiber from the cannula 40.

Methods of forming an implant in a body are discussed below with reference to FIGS. 1–4, 5*a*, 5*b*, and 6–8. Although the invention is described in connection with the structure shown in these figures, it should be understood that the invention in its broadest sense is not so limited.

Initially, the distal end portion of the cannula 40 shown in FIGS. 1 and 2 is inserted in the body of a patient and the distal end is guided to a site where the implant is to be formed. To facilitate the insertion, a guide wire is inserted in the first lumen 54 and the cannula 40 is moved over the guide wire. In addition, the movement of the cannula 40 can be monitored fluoroscopically.

When the cannula is properly positioned, the syringe 20 is coupled to the adapter 42. Then, the plungers 26 and 28 are moved simultaneously in the barrels 22 and 24 to eject the first and second liquids respectively through the lumens 54 and 56 and into the mixing chamber 60. In the mixing chamber 60, the polysaccharide, such as alginate, and the ionic cross linking agent mix, and the ions of the cross linking agent cross link with the polysaccharide to form the cross linked polysaccharide fiber in the mixing chamber 60. For example, when the first liquid includes sodium alginate and the second liquid includes calcium chloride, a cross linked alginate fiber forms in the mixing chamber 60. The resulting fiber is flexible and has an outer surface matching the inner surface of the second tubular portion 52. As the fiber is formed, the fiber is ejected from the cannula 40 via the opening 58.

Since the fiber is formed inside the cannula 40, the fiber is one continuous piece as it is injected into a vessel or a cavity. If the injection of both the first and second liquids continue, the fiber continues to form as one piece and is extruded out the end of the cannula 40. This allows the fiber to stay together and reduces the chance of embolization. As the fiber passes from the cannula 40, the fiber contacts tissue and curls up on itself inside the cavity it is filling to form a ball or nest shaped implant structure. Preferably, the consistency of the cross linked alginate fiber is soft enough to allow dense packing inside the cavity.

As mentioned above, an agent, such as tantalum, tungsten, barium sulfate, and/or titanium dioxide, can be added to at least one of the first and second liquids to make the resulting fiber radiopaque. As the fiber is formed, a procedurist can monitor the formation and implantation of the fiber via imaging equipment.

The fiber can be delivered via the cannula 40, shown in FIGS. 1 and 2, or the cannula 40*a*, shown in FIG. 3, into a blood vessel to occlude the vessel partially or completely. For example, the fiber could be delivered into a blood vessel leading to an aneurysm to limit blood flow to the aneurysm by occluding the vessel. The fiber could also be used to treat an AVM by delivering the fiber into a vessel leading to the AVM to limit blood flow to the AVM.

In a preferred method, the distal end of the cannula 40, shown in FIGS. 1 and 2, or the cannula 40*a*, shown in FIG. 3, is placed adjacent to an aneurysm and the cross linked fiber is ejected to fill the sac or cavity of the aneurysm at least partially. When the fiber contacts tissue in the cavity it curls back on itself making a ball or nest of fiber that provides packing in the cavity. This ball or nest of fiber is able to fill an irregularly shaped sac completely. When the fiber includes alginate, the alginate material provides a biocompatible surface at the aneurysm neck for endothelial cell growth. In addition, the fiber mass limits blood flow to the aneurysm and protects the fragile aneurysm wall from rupturing since it is no longer exposed to the hemodynamic forces of the normal pulsatile blood flow.

Preferably, the first liquid and/or the second liquid include a precipitating material or an adhesive when the fiber is delivered to fill an aneurysm sac or cavity. The precipitating material forms a matrix for holding the fiber implant together, and the adhesive adheres portions of the fiber to one another. This maintains the implant in the sac and prevents fiber migration in the body.

Because the fiber is flexible, the nest or ball of fiber is more dense than a rigid metal coil and fills a higher percentage of volume of the blood vessel or the aneurysm cavity. As mentioned above, a thrombogenic substance can be added to one of the first and second liquids. When a fiber having this substance is implanted in an aneurysm cavity, it releases the thrombogenic substance to induce thrombosis in the cavity.

As compared to some gels used to fill aneurysms, it is easier to control the volume of fiber. In addition, the fiber fills the cavity more completely to minimize leakage and may take up more volume than beads of gel. Also, the fiber preferably does not embolize rapidly.

In another method, the distal end of the cannula 40, shown in FIGS. 1 and 2, or the cannula 40*a*, shown in FIG. 3, is inserted into the body and used to deliver the fiber into soft tissue to provide bulking of the soft tissue. For example, the fiber could be delivered next to the urethral sphincter to provide bulking for the treatment of bladder incontinence.

The dual barrel syringe **20** shown in FIG. **2** allows for constant infusion of both the first liquid and the second liquid to the mixing chamber **60** shown in FIG. **1**. Because the fiber is formed in the mixing chamber **60** of the cannula **20** itself, there is no need to manufacture the fiber separately, install it in a delivery device, and use a carrier fluid.

When using the system **10** shown in FIGS. **1** and **2**, the length of fiber filling the body cavity does not need to be pre-determined. The fiber continues to form as long as the first and second liquids are injected. The cutter **82** shown in FIGS. **4**, **5***a*, and **5***b* or the cutter **82***c* shown in FIGS. **6–8** can be used to sever the implanted portion of the fiber from the portion of fiber residing in the mixing chamber **60**. When the first tubular portion **50**, shown in FIGS. **1** and **2**, is axially movable in the second tubular portion **52**, the first tubular portion **50** may be moved axially toward the distal opening **58** to push the formed fiber from the mixing chamber **60** and thereby separate the fiber from the cannula **40**.

A method of forming a fiber is discussed below with reference to FIG. **9**. Although this aspect of the invention is described in connection with the structure shown in this figure, it should be understood that the invention in its broadest sense is not so limited.

FIG. **9** shows a tubular member **94** and a reservoir **96** used in the manufacture of a cross linked polysaccharide fiber for the system **10***a* shown in FIG. **3** or for one of the fiber delivery devices disclosed in above-mentioned U.S. patent application Ser. No. 08/776,943. The tubular member **94** is coupled to a source of liquid including polysaccharide, such as a liquid including alginate (sodium alginate), and the reservoir **96** contains a liquid including an ionic cross linking agent, such as a liquid including calcium chloride or a liquid solution including other divalent cations.

The liquid including polysaccharide flows through the tubular member **94** and into the liquid including cross linking agent in the reservoir **96** via an opening in a distal end portion of the tubular member **94**. As the liquid including polysaccharide flows from the tubular member **94** and contacts the cross linking agent, the cross linked polysaccharide fiber forms. The formed fiber has an outer surface shape similar to the inner surface shape of the opening and lumen in the tubular member **94**. When the fiber increases in length, it can be wound on a spool, such as the spool **62** shown in FIG. **3**, and then loaded in a delivery device, such as the system **10***a* shown in FIG. **3**, or one of the fiber delivery devices disclosed in above-mentioned U.S. patent application Ser. No. 08/776,943.

Varying the size of the tubular member **94** and flow of the liquid in the tubular member **94** can control the composition, size, and consistency of the cross-linked fiber. Radiopaque substances can be added to the liquid flowing in the tubular member **94** and/or to the liquid in the reservoir **96** to render the cross linked fiber radiopaque. In addition, one or more drugs can be added to one or both liquids to enable drug delivery via the formed fiber. Chitosan can also be added to one or both of the liquid to provide structural integrity to the fiber.

It will be apparent to those skilled in the art that various modifications and variations can be made to the structure and methodology of the present invention without departing from the scope or spirit of the invention. In view of the foregoing, it is intended that the present invention cover modifications and variations of this invention provided they fall within the scope of the following claims and their equivalents.

What is claimed is:

1. A device for delivery of a fiber in a body, comprising:

a cannula having a lumen and an opening in a distal end portion of the cannula;

a fiber designed to be passed from the lumen into the body through the opening in the cannula; and

a cutter for severing the fiber when the fiber passes from the lumen into the body through the opening in the cannula, the cutter including

a loop shaped portion for surrounding a fiber when the fiber passes through the lumen and the opening, and

an actuator extending from the loop shaped portion, movement of the actuator forcing the loop shape portion through the fiber to sever the fiber.

2. The device of claim **1**, wherein the cannula includes an auxiliary lumen, the actuator passing through the auxiliary lumen.

3. The device of claim **1**, further comprising a reservoir capable of forming the fiber.

4. The device of claim **1**, wherein portions of the fiber adhere to one another.

5. The device of claim **1**, further comprising means for forming the fiber.

6. The device of claim **1**, further comprising a first reservoir containing a first liquid and a second reservoir containing a second liquid, the first and second liquids being capable of forming the fiber.

7. The device of claim **6**, wherein the cannula includes a first lumen in fluid communication with the first liquid in the first reservoir and a second lumen in fluid communication with the second liquid in the second reservoir.

8. A device for delivery of a fiber in a body, comprising:

a cannula having a lumen and an opening in a distal end portion of the cannula means for forming a fiber; and

a cutter for severing a fiber passing through the lumen and the opening, the cutter including

a loop shaped portion for surrounding a fiber when the fiber passes through the lumen and the opening, and

an actuator extending from the loop shaped portion, movement of the actuator forcing the loop shape portion through the fiber to sever the fiber.

9. A device for delivery of a fiber in a body comprising:

a cannula having a lumen and an opening in a distal end portion of the cannula;

a first reservoir containing a first liquid and a second reservoir containing a second liquid, the first and second liquids being capable of forming a fiber; and

a cutter for severing a fiber passing through the lumen and the opening, the cutter including

a loop shaped portion for surrounding a fiber when the fiber passes through the lumen and the opening, and

an actuator extending from the loop shaped portion, movement of the actuator forcing the loop shape portion through the fiber to sever the fiber.

10. The device of claim **9** , wherein the cannula includes a first lumen in fluid communication with the first liquid in the first reservoir and a second lumen in fluid communication with the second liquid in the second reservoir.

11. A device for delivery of a fiber in a body, comprising:

a cannula having a lumen and an opening in a distal end portion of the cannula a fiber for passage through the lumen, said fiber being at least partially in the lumen; and

a cutter for severing the fiber when the fiber passes through the lumen and the opening the cutter including

a loop shaped portion for surrounding the fiber when the fiber passes though the lumen and the opening, and

an actuator extending from the loop shaped portion, movement of the actuator forcing the loop shape portion through the fiber to sever the fiber.

12. The device of claim **11**, further comprising a reservoir capable of forming the fiber.

13. A device for delivery of a fiber in a body, comprising:

a cannula having a lumen and an opening in a distal end portion of the cannula;

a fiber for passage through the lumen, said fiber being for formed of cross-linked materials; and

a cutter for severing the fiber when the fiber passes through the lumen and the opening, the cutter including

a loop shaped portion for surrounding the fiber when the fiber passes through the lumen and the opening, and

an actuator extending from the loop shaped portion, movement of the actuator forcing the loop shape portion through the fiber to sever the fiber.

14. The device of claim **13**, wherein the fiber is formed by mixing a first liquid and a second liquid.

15. The device of claim **14**, wherein the first liquid includes a polysaccharide and the second liquid includes an ionic cross-linking agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,258,055 B1
DATED : July 10, 2001
INVENTOR(S) : Jennifer McCrory et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10, claim 8,
Line 37, after "portion of the cannula", insert -- ; --, and insert a line break immediately thereafter.

Column 10, claim 9,
Line 45, after "body", insert -- , --.

Column 10, claim 10,
Line 59, replace "claim 9," with -- claim 9, --.

Column 10, claim 11,
Line 65, after "portion of the cannula", insert -- ; --, and insert a line break immediately thereafter.

Column 11, claim 11,
Line 2, after "opening", insert -- , --.

Column 11, claim 13,
Line 14, after "fiber being", delete "for".

Signed and Sealed this

Twenty-sixth Day of February, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US-PAT-NO: 6258055

DOCUMENT-IDENTIFIER: US 6258055 B1
See image for Certificate of Correction

TITLE: System for implanting a cross-linked polysaccharide fiber and methods of forming and inserting the fiber

---------- KWIC ---------

INVENTOR - INNM (4):
Sahatjian; Ronald

Inventor Group - INGP (4):
Sahatjian; Ronald Lexington MA

Brief Summary Text - BSTX (5):
Alginate is a polysaccharide material derived from brown seaweed. Although the predominate use of alginates is as a food additive to thicken and stabilize solutions, they are also used in various medical applications. Alginate can be easily cross linked into biocompatible hydrogels used as a cell immobilization matrix for various biotechnology applications. In addition, this substance can be used as a biodegradable gel/film coating in pharmaceutical applications. Alginate is also used to make wound dressings and pads capable of absorbing wound exudate and providing a moisture permeable wound covering.

Detailed Description Text - DETX (13):
Preferably, the first liquid contained in the first barrel 22 of the syringe 20 is a solution including a polysaccharide, such as sodium alginate , and the

second liquid contained in the second barrel 24 of the syringe 20 is a solution including an ionic cross linking agent, such as calcium (i.e. calcium chloride) or some other cross linking agent having divalent ions. For example, when sodium alginate and calcium chloride combine in the mixing chamber 60, the divalent cations (calcium ions) replace the sodium ions to form a cross linked, hydrogel, alginate fiber. Because the resulting cross linked alginate fiber is a hydrogel, it is possible to capture certain contrast substances into the gel to make the fiber visible in MRI, CT, and fluoroscopy.

US-PAT-NO: 6152141

DOCUMENT-IDENTIFIER: US 6152141 A

TITLE: Method for delivery of therapeutic agents to the heart

---------- KWIC ---------

Brief Summary Text - BSTX (20):
To ensure a longer duration of contact between the VEGF and the myocardium to further stimulate angiogenesis, the vascular endothelial growth factors may be suspended in a viscous liquid, such as a fibrin based glue or a bioabsorbable polymer gel. These viscous liquids have a greater likelihood of extended exposure to the treated regions where a longer exposure duration to VEGF may be advantageous.

Detailed Description Text - DETX (21):
The stent 548 is preferably impregnated with a therapeutic agent for delivery to the myocardium in a timed release manner. The stent is preferably composed of a conventional stent material such as stainless steel, NiTi or other shape memory alloys. A bioabsorbable coating 551, impregnated with the desired agent, is coated over stent 548 so that the agent can be absorbed into the myocardium through the coronary artery wall. Accordingly, once the stent 548 is properly positioned and expanded in the coronary artery 51 to dilate the stenosis 102 (FIG. 14C), the timed release of the agent directly to the vasculature of the myocardium can commence. Suitable bioabsorbable coatings may include fibrin based glues, absorbable polymers, and ethylene vinyl acetate

copolymers, waxes, hydrophilic gums, hydrogels, poly(othoesters), poly(orthocarbonates). Other bioabsorbable coatings suitable for use with the present invention are disclosed in U.S. Pat. No. 5,518,730, hereby incorporated by reference. Alternatively, stent 548 itself may be composed of a bioabsorbable material which is impregnated with a therapeutic agent. Examples of balloons suitable for expanding a coronary artery stent are described in U.S. Pat. Nos. 5,055,024 and 4,490,421 which are hereby incorporated by reference,. Examples of arterial stents and stent delivery catheters are described in U.S. Pat. Nos. 5,041,126, 4,856,516 and 5,037,392 which are hereby incorporated by reference.

Detailed Description Text - DETX (27):

Referring now to FIGS. 19 and 20, an alternative method for delivering a therapeutic agent directly to the epicardial surface 104 of the heart 100 is provided using thoracoscopic techniques. As stated above, timed release of VEGF to a TMR treatment site may have more long term success in stimulating angiogenesis. In contrast, a one dose regimen of VEGF may be absorbed and dissipated too rapidly in the body for effective exposure at the treatment site. One technique to increase the duration of VEGF stimulation is to suspend the VEGF in a substance capable of timed release delivery of the VEGF to the myocardium. Such an extended dosage regimen, accordingly, increases the likelihood of a successful exposure between the VEGF and the TMR treatment site. A topical solution, for example, may be applied directly to the epicardial surface of the heart. This substance may include a fibrin based glue or a biocompatible gel which continuously delivers the VEGF in a timed

release manner up to about 25-30 days after the initial application.
Alternatively, the VEGF could be encapsulated in a bioabsorbable polymer gel,
viscous fluid or mixture of a solid and viscous fluid (slurry) that could
release the VEGF over a longer duration of time up to about 2 years.
Appropriate polymer gels include absorbable polymers based on polyanhydrides,
polycaprolactone, lactide, glycolide, polydioxanone and blends, and copolymers
of the former. Topical application of agents, such as VEGF, may also be
delivered pericardialy, intramyocardialy, or intrapericardialy.

US Reference Patentee Name - URNM (25):
Sahatjian

US Reference Group - URGP (25):
5533516 19960700 Sahatjian

Other Reference Publication - OREF (11):
Kissel et al., "Parental Depot-systems on the Basis of Biodegradable
Polyesters," Journal of Controlled Substances, 1991;16:27-41.

US-PAT-NO: 6152141

DOCUMENT-IDENTIFIER: US 6152141 A

TITLE: Method for delivery of therapeutic agents to the heart

---------- KWIC ---------

Brief Summary Text - BSTX (20):
To ensure a longer duration of contact between the VEGF and the myocardium to further stimulate angiogenesis, the vascular endothelial growth factors may be suspended in a viscous liquid, such as a fibrin based glue or a bioabsorbable polymer gel. These viscous liquids have a greater likelihood of extended exposure to the treated regions where a longer exposure duration to VEGF may be advantageous.

Detailed Description Text - DETX (21):
The stent 548 is preferably impregnated with a therapeutic agent for delivery to the myocardium in a timed release manner. The stent is preferably composed of a conventional stent material such as stainless steel, NiTi or other shape memory alloys. A bioabsorbable coating 551, impregnated with the desired agent, is coated over stent 548 so that the agent can be absorbed into the myocardium through the coronary artery wall. Accordingly, once the stent 548 is properly positioned and expanded in the coronary artery 51 to dilate the stenosis 102 (FIG. 14C), the timed release of the agent directly to the vasculature of the myocardium can commence. Suitable bioabsorbable coatings may include fibrin based glues, absorbable polymers, and ethylene vinyl acetate

copolymers, waxes, hydrophilic gums, hydrogels, poly(othoesters), poly(orthocarbonates). Other bioabsorbable coatings suitable for use with the present invention are disclosed in U.S. Pat. No. 5,518,730, hereby incorporated by reference. Alternatively, stent 548 itself may be composed of a bioabsorbable material which is impregnated with a therapeutic agent. Examples of balloons suitable for expanding a coronary artery stent are described in U.S. Pat. Nos. 5,055,024 and 4,490,421 which are hereby incorporated by reference,. Examples of arterial stents and stent delivery catheters are described in U.S. Pat. Nos. 5,041,126, 4,856,516 and 5,037,392 which are hereby incorporated by reference.

Detailed Description Text - DETX (27):

Referring now to FIGS. 19 and 20, an alternative method for delivering a therapeutic agent directly to the epicardial surface 104 of the heart 100 is provided using thoracoscopic techniques. As stated above, timed release of VEGF to a TMR treatment site may have more long term success in stimulating angiogenesis. In contrast, a one dose regimen of VEGF may be absorbed and dissipated too rapidly in the body for effective exposure at the treatment site. One technique to increase the duration of VEGF stimulation is to suspend the VEGF in a substance capable of timed release delivery of the VEGF to the myocardium. Such an extended dosage regimen, accordingly, increases the likelihood of a successful exposure between the VEGF and the TMR treatment site. A topical solution, for example, may be applied directly to the epicardial surface of the heart. This substance may include a fibrin based glue or a biocompatible gel which continuously delivers the VEGF in a timed

release manner up to about 25-30 days after the initial application.
Alternatively, the VEGF could be encapsulated in a bioabsorbable polymer gel,
viscous fluid or mixture of a solid and viscous fluid (slurry) that could
release the VEGF over a longer duration of time up to about 2 years.
Appropriate polymer gels include absorbable polymers based on polyanhydrides,
polycaprolactone, lactide, glycolide, polydioxanone and blends, and copolymers
of the former. Topical application of agents, such as VEGF, may also be
delivered pericardialy, intramyocardialy, or intrapericardialy.

US Reference Patentee Name - URNM (25):
Sahatjian

US Reference Group - URGP (25):
5533516 19960700 Sahatjian

Other Reference Publication - OREF (11):
Kissel et al., "Parental Depot-systems on the Basis of Biodegradable
Polyesters," Journal of Controlled Substances, 1991;16:27-41.

US-PAT-NO: 5304121

DOCUMENT-IDENTIFIER: US 5304121 A
See image for Certificate of Correction

TITLE: Drug delivery system making use of a hydrogel polymer coating

---------- KWIC ---------

Abstract Text - ABTX (1):
The invention features a catheter and methods for delivering drug to tissue at a desired location of the wall of a body lumen. The catheter is constructed for insertion in a body lumen and has a catheter shaft and an expandable portion mounted on the catheter shaft. The expandable portion is expandable to a controlled pressure to fill the cross-section of the body lumen and press against the wall of the body lumen. In one embodiment, at least a portion of the exterior surface of the expandable portion is defined by a coating of a tenaciously adhered swellable hydrogel polymer. Incorporated in the hydrogel polymer is an aqueous solution of a preselected drug to be delivered to the tissue or plaque. The hydrogel polymer and drug are selected to allow rapid release of a desired dosage of the drug from the hydrogel polymer coating during compression of the hydrogel polymer coating against the wall of the lumen when the expandable portion is expanded. In other embodiments the polymer is released from the expandable portion in response to pressure, to coat the wall of the body lumen.

TITLE - TI (1):

Drug delivery system making use of a hydrogel polymer coating

INVENTOR - INNM (1):
Sahatjian; Ronald

Inventor Group - INGP (1):
Sahatjian; Ronald Lexington MA

Brief Summary Text - BSTX (8):

In one aspect, the invention features a catheter and method for delivering drug to tissue at a desired location of the wall of a body lumen. The catheter is constructed for insertion in a body lumen and has a catheter shaft and an expandable portion mounted on the catheter shaft. The expandable portion is expandable to a controlled pressure to fill the cross-section of the body lumen and press against the wall of the body lumen. At least a portion of the exterior surface of the expandable portion is defined by a coating of a tenaciously adhered swellable hydrogel polymer. Incorporated in the hydrogel polymer is an aqueous solution of a preselected drug to be delivered to the tissue. The hydrogel polymer and drug are selected to allow rapid release of a desired dosage of the drug from the hydrogel polymer coating during compression of the hydrogel polymer coating against the wall of the lumen when the expandable portion is expanded.

Brief Summary Text - BSTX (9):

Various embodiments may include one or more of the following features. The catheter is adapted for insertion in a blood vessel, and the expandable portion is an inflatable dilatation balloon adapted for inflation at pressures in the range for effecting widening of a stenosed blood vessel.

The pressure is in the range of about 1 to 20 atmospheres. The hydrogel polymer and drug are effective to release about 20% or more of the drug during inflation in the pressure range. The compression is effective to deliver the drug over a duration of about 10 minutes or less. The hydrogel polymer coating is about 10 to 50 microns thick in the swelled, uncompressed state. The hydrogel polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, and polyethylene oxides. The hydrogel polymer is polyacrylic acid. The drug is an anti-thrombogenic drug selected from the group consisting of heparin, PPack, enoxaprin, aspirin and hirudin. The drug is an anti-proliferative drug selected from the group consisting of monoclonal antibodies, capable of blocking smooth muscle cell proliferation, heparin, angiopeptin and enoxaprin. The expandable portion is adapted for application of heat to the polymer material to control the rate of administration. The catheter further comprises a sheath member, extendable over the balloon to inhibit release of the drug into body fluids during placement of the catheter.

The balloon catheter is a perfusion catheter having an expandable balloon. The expandable portion includes a stent, mountable in the blood vessel by expansion thereof. The drug is bound in the hydrogel polymer for slow time release of the drug after the compression of the hydrogel polymer by the expansion. The hydrogel polymer is a polyacrylic acid including an ammonium anion and the drug is heparin. The stent is expandable by a balloon. The catheter where the stent and balloon both include the swellable hydrogel coating incorporating the drug. The expandable portion is prepared by introducing an

aqueous solution of
the drug to the hydrogel polymer coating, the catheter is introduced to the
body lumen to position the expandable portion at the point of desired drug
application, and the expandable portion is expanded to enable delivery of the
drug by compression of the hydrogel polymer coating against the wall at the
body lumen. The expandable portion is positioned at a point of occlusion in
the blood vessel and expanding the expandable portion at pressures sufficient
to simultaneously dilate the vessel and deliver the drug by compression of the
hydrogel polymer coating.

Brief Summary Text - BSTX (10):

In a particular aspect, the invention includes a balloon catheter for
delivering drug to tissue at a desired location of the wall of a blood vessel.
The catheter is constructed for insertion in a blood vessel and has a catheter
shaft and an expandable dilatation balloon mounted on the catheter shaft. The
expandable balloon is expandable by an expansion controller to engage the
tissue at a controlled pressure in the range of about 1 to 20 atmospheres to
fill the cross-section of the blood vessel and press against the wall of the
blood vessel. At least a portion of the exterior surface of the expandable
balloon is defined by a coating of a tenaciously adhered swellable hydrogel
polymer with a thickness in the range of about 10 to 50 microns in the swelled
state, and incorporated within the hydrogel polymer coating, an aqueous
solution of a preselected drug to be delivered to the tissue. The hydrogel
polymer and drug are selected to allow rapid release of a desired dosage of
about 20% or more of the drug solution from the hydrogel polymer coating during
compression of the hydrogel polymer coating against the

wall of the vessel when
the expandable portion is expanded in the pressure range.

Brief Summary Text - BSTX (11):
In various embodiments, the hydrogel polymer is selected from the group
consisting of polycarboxylic acids, cellulosic polymers, gelatin,
polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl
alcohols, and polyethylene oxides. The hydrogel polymer is polyacrylic acid.
The drug is an anti-thrombogenic drug selected from the group consisting of
heparin, PPack enoxaprin, aspirin and hirudin. The drug is an
anti-proliferative drug selected from the group consisting of monoclonal
antibodies, capable of blocking smooth muscle cell proliferation, heparin,
angiopeptin and enoxaprin. The catheter further comprises a sheath member,
extendable over the balloon to inhibit release of the drug into body fluids
during placement of the catheter.

Drawing Description Text - DRTX (13):
FIG. 4 shows a balloon catheter with the hydrogel and drug coated
endoprosthesis mounted on the balloon section, in the region of the thrombus,
before radial expansion of the balloon section and endoprosthesis.

Drawing Description Text - DRTX (14):
FIG. 4a is an enlargement of FIG. 4 showing the hydrogel polymer and drug
coated endoprosthesis and FIG. 4b is a cross-section along the line b--b in
FIG. 4a.

Detailed Description Text - DETX (2):
Referring to FIGS. 1-1e, in one embodiment, the invention includes a drug

delivery balloon catheter device 1 comprising a catheter body 3 having a balloon 4 attached at its distal end. The balloon 4 on the catheter 3 includes a swellable hydrogel polymer coating 6. As shown in FIGS. 1-1a, a drug 8 in an aqueous solution is absorbed into the hydrogel with the balloon in the deflated state prior to insertion into the patient by the physician, e.g., the hydrogel-coated balloon may be immersed in a small tube or vial containing the drug. The drug may also be applied in the form of droplets, such as from an eyedropper, or the drug may be precipitated into the hydrogel prior to sterilization and sold as a finished device. Exposure of the hydrogel to the solution causes the hydrogel to swell.

Detailed Description Text - DETX (3):

As shown in FIG. 1b, typically the device 1 is inserted into the duct or vessel 2 having a region to be treated, such as an occlusion due to a deposition of plaque 5 on the vessel wall tissue 9. The device I is moved along the vessel to position the balloon 4 at the occlusion site, as shown in FIG. 1c. The vessel may be, for example, a narrow, tortuous opening through which the catheter is passed by torquing from the distal end. As the balloon is inflated the pressure created by the balloon against the tissue compresses the hydrogel and the drug is quickly and freely released for transfer by active diffusion into the plaque and tissue. The pressure applied to the plaque and tissue by the expansion of the balloon during application of the drug enhances transfer of the drug into the tissue and plaque. This process is referred to here as active diffusion. The balloon and catheter may be exposed to the body fluids of the lumen for a considerable time, e.g., up to about 15 minutes in

some angioplasty procedures. An advantage of this invention is that large amounts of the drug, e.g., greater than 20%, even 30-50% or more, of the drug solution contained in the hydrogel, is diffused into the effected area in the short time duration which the hydrogel is compressed, e.g., 2-10 minutes after the balloon is inflated at the treatment site. The inflation pressure needed to dilate the vessel which also approximates the compression of the coating, is in the range of 1 to 20, typically about 2 to 10 atmospheres. The balloon is preferably a compliant material such as polyethylene which conforms to the shape of the lumen wall. The balloon may also be formed of other materials used in angioplasty, e.g., a nondistending material, such as polyethylene terephthalate (PET). Transporting the drug in the hydrogel prevents substantial release of the drug to body fluids prior to reaching the treatment area and during the drug application phase and allows large dosages to be delivered at a desired location.

Detailed Description Text - DETX (4):

In the embodiment of FIG. 1c, the balloon coating 6 is a swellable, compressible coating formed of the hydrogel and drug in solution. In FIG. 1d, the balloon 4 is shown inflated such that the coating 6, which has an initial thickness, is in contact with the occlusion 5 but not under substantial pressure. Further inflation of the balloon 4, as shown in FIG. 1e, compresses the hydrogel coating 6 against the occluded areas 5 causing quick release of the drug (represented by circles) contained in the coating 6 directly into the plaque and nearby healthy tissue, as indicated by the directional arrows, much in the nature of squeezing liquid from a sponge. The introduction of the drug

into the plaque and tissue occurs simultaneously with widening of the occlusion by the dilatation balloon. Thus, as cracking of the plaque and stimulation of smooth muscle cells beneath the plaque and along healthy tissue of the vessel wall are caused by dilatation, a therapeutic drug is simultaneously applied to the effected area, e.g., to counteract the effects of the trauma. The thickness of the balloon 4 remains substantially the same, while the thickness of the coating 6 decreases due to the compression of the coating and the release of the drug 8. (FIGS. 1d-1e are schematic drawings and are not to scale with respect to the thickness of the balloon relative to the thickness of the hydrogel coating.) The drug carried by the balloon is evenly applied to plaque and tissue and isolated by the pressure of the balloon from the flow of body fluids in the lumen such that the drug, e.g., an anti-proliferative, may actively diffuse through the cracks formed in the plaque and reach the smooth muscle tissue. (It will also be understood that, as an alternative procedure, after dilation with a conventional angioplasty balloon catheter, a catheter carrying a drug-delivery, inflatable balloon, such as has been described, may be used to treat the vessel.)

Detailed Description Text - DETX (5):

The hydrogel coating is characterized by the ability to incorporate a substantial amount of the drug, typically in aqueous solution form, and is swellable such that the aqueous drug solution can be effectively squeezed out of the coating when pressure is applied by inflation of the balloon. Administration of the drug in this way enables the drug to be site specific, such that release of high concentrations and/or highly potent drugs may be

limited to direct application to the diseased tissue. Furthermore, the drug is applied to the diseased tissue by the sponge-like coating in an even, gentle manner without disrupting or injuring the healthy tissue, while diffusion of the drug into the tissue is facilitated by the application of the pressure of the inflated balloon. The pressure also effectively forms a seal that prevents the flow of body fluids from washing the drug downstream of the treatment area. The dosage applied to the tissue may be controlled by regulating the time of presoaking the drug into the hydrogel coating to determine the amount of absorption of the drug solution by the hydrogel coating. Other factors affecting the dosage are the concentration of the drug in the solution applied to the coating and the releasability of the hydrogel coating, determined by, for example, the thickness of the hydrogel coating, its resiliency, porosity and the ability of the hydrogel coating to retain the drug, e.g., electrostatic binding or pore size, or the ionic strength of the coating, e.g., changed by changing the pH.

Detailed Description Text - DETX (6):

The drug may be an anti-thrombogenic drug, such as heparin or a heparin derivative, PPack (dextrophenylalanine proline arginine chloromethylketone) or an anti-proliferative, such as heparin (also known to have anti-proliferative properties), enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, or it may be hirudin or acetylsalicylic acid (i.e., aspirin). Dosages applied to the tissue, for example, of heparin are typically in the range of 10-30 mg of heparin solution containing 200-1,000 units of sodium heparin. For use with hydrogels, the drug

is preferably water soluble, so that the drug may be easily absorbed into the
coating matrix.

Detailed Description Text - DETX (7):
The sponge-like characteristics of the hydrogel allows the aqueous drug
solution to be effectively squeezed out of the coating when pressure is applied
by inflation of the balloon. The hydrogel and drug combination are preferably
noncomplexed, i.e., held together through the ability of the hydrogel to swell
and absorb the drug solution, thereby allowing the preferable free-release of
the drug at the treatment site.

Detailed Description Text - DETX (8):
In particular embodiments it may be advantageous to select a hydrogel
coating for a particular drug such that the drug is not substantially released
into body fluids prior to application of pressure by expansion of the balloon.
Binding of the drug may also be accomplished by electrostatic attraction of the
drug to the coating or a coating additive or by mechanical binding, e.g.,
employing a coating having a pore size that inhibits inward flow of body fluids
or outward flow of the drug itself, that might tend to release the drug.
Hydrogels are particularly advantageous in that the drug is held within the
hydrogen-bond matrix formed by the gel.

Detailed Description Text - DETX (9):
The hydrogel is a cross-linked polymer material formed from the combination
of a colloid and water. Cross-linking reduces solubility and produces a
jelly-like polymer that is characterized by the ability to swell and absorb a
substantial amount of the drug, typically in aqueous solution form. The

hydrogel coating is also particularly hydrophilic, water swellable, and lubricous (i.e., having a low coefficient of friction). Preferred hydrogels are polyacrylic acid polymers available as HYDROPLUS.RTM. (Boston Scientific, Watertown, Mass.) and as described in U.S. Pat. No. 5,091,205, the portion disclosed in the parent application to this patent being incorporated by reference). The drug, e.g., heparin in aqueous solution, is absorbed into the coating without complexing and is freely released therefrom. Such hydrogel-drug combinations deliver about half of the drug solution in response to pressures in the range of balloon angioplasty in the vascular system. In other particular embodiments, the hydrogel polymer includes acid groups and incorporates a drug which is anionic in nature that is bound by electrostatic attraction to cations in the coating, such as an ammonium cation, as described in "Lubricous Antithrombogenic Catheters, Guidewires, and Coatings " by Ronald Sahatjian et al, U.S. Pat. No,. 5,135,516, the entire contents of which are hereby incorporated by reference. The coating incorporating the quaternary ammonium salt is effective to deliver an initial fast release of drug during compression and a slow release of drug remaining in the compressed coating after compression and is particularly useful for coating vascular stents as described further below.

Detailed Description Text - DETX (10):

In general, when dry, the hydrogel coating is preferably on the order of about 1 to 10 microns thick, with a 2 to 5 micron coating typical. Very thin hydrogel coatings, e.g., of about 0.2-0.3 microns (dry) and much thicker hydrogel coatings, e.g., more than 10 microns (dry), are also possible.

Typically, the hydrogel coating thickness may swell by about a factor of 6 to 10 or more when the hydrogel coating is hydrated. For example, a hydrogel coating of about 1 to 3 microns thickness, when dry, usually swells to about 10-30 microns thickness, when hydrated. Most preferably, the thickness of the coating is about 10 to 50 microns in the swelled, uncompressed state, and incorporates about 20-30 mg of drug solution.

Detailed Description Text - DETX (12):

A procedure for preparing a drug delivery balloon with a hydrogel coating and an experiment of drug delivery for the above embodiments are presented in the following examples.

Detailed Description Text - DETX (15):

A hydrogel coating on an angioplasty balloon may be formed as follows. The surface of the balloon (polyethylene) of an angiographic catheter is prepared by wiping down with clean cloth. The balloon has an O.D. (outer diameter) of about 3.5 mm (inflated). The balloon is coated with a solution of 4,4' diphenylmethane diisocyanate (MDI) in methylethylketone for 30 minutes. After drying in an air oven at 85.degree. C. for 30 minutes, the balloon is dipped in a 1.7% solution of poly(acrylic acid) homopolymer having a molecular weight of about 3,000,000 in dimethylformamide (DMF) and tertiarybutyl alcohol. After drying at about 85.degree. C. for 30 minutes, a smooth coating is obtained. The balloon is oven dried for 8 hours at 50.degree. C. One function of the drying steps is to remove solvent from the coating. The surface of the balloon becomes instantly lubricous upon exposure to water. The polyisocyanate solution is at a concentration of about 0.5 to 10% by weight. The polyacrylic

acid is at a concentration of about 0.1 to 10% by weight. The poly(carboxylic acid) to polyisocyanate molar ratio is generally about 1:1. The formation of the hydrogen is further described in U.S. Pat. No. 5,091,205 incorporated supra.

Detailed Description Text - DETX (16):

A solution of heparin salt may be applied to the coating. The solution is 10,000 units heparin sodium injection (Fisher Scientific, Pittsburgh, Pa.) USP Grade (1000 units/ml which is then added to 650 cc distilled water) and may be applied by dipping for, e.g., about 1 minute at room temperature. The heparin does not form a complex with the hydrogel solution and is freely released in response to compression of the polymer.

Detailed Description Text - DETX (17):

After a catheter is prepared for use as discussed above, the catheter may be introduced into the patient using the Seldinger technique and expanded at a desired location to compress the hydrogel and deliver the heparin solution.

Detailed Description Text - DETX (19):

Delivery of a drug from a hydrogel coating on a balloon was investigated in the following experiment. Tritium-labeled Pebac was absorbed into a 3.5 mm Slider.RTM. (balloon catheter from Boston Scientific Corporation) balloon coated with about a 40 micron thick (in the swelled state) coating as described in Example 1. The coating was dried and the radioactivity was counted. The balloon was then wetted with saline to swell the coating area. The balloon was inflated over a period of about one minute to about 4 atmospheres and held at this pressure for about 10 minutes in a thrombus created in

an AV shunt from a baboon. The balloon was withdrawn and the amount of the drug in the thrombus was counted with a radiation counter. The experiment was performed with two different balloons using two different concentrations of PPack, balloon with 1-2 mg Pebac, and one balloon with 4 mg Pebac. Both balloons delivered about 50% of the Pebac into the thrombus.

Detailed Description Text - DETX (22):

An advantage to the meltable coatings is that the polymer may be cross-linked, (e.g., by physical or chemical cross-linking) after application of the drug 44 to the balloon to inhibit release of the drug 44 as the balloon 42 is introduced through the body lumen to the area of treatment. The polymer itself typically does not melt off the balloon, but rather softens in a manner permitting release. However, in embodiments where the polymer is bioabsorbable, e.g., polycaprolactone, polyorthoesters, polylactic acids, and polyglycolic acids, some or even all of the polymer may dissolve off of the balloon.

Detailed Description Text - DETX (23):

The balloon may also be coated with a polymer incorporating a drug and inflated to press against the wall of the body lumen, where the polymer is selected to separate from the balloon and coat the wall of the lumen, in response to such pressure with or without the application of heat from the balloon. After application of the polymer, the balloon can be deflated and removed. In this embodiment, the polymer may be a blood soluble polymer such as albumin, collagen or the like, incorporating a drug such as heparin. The polymer produces a smooth coating on the wall of the lumen

and releases the
drug to the tissue over time as the polymer dissolves.
Other soluble polymers
are meltable and bioabsorbable polymers discussed above.

Detailed Description Text - DETX (24):
In another embodiment (see FIGS. 4-6) an endoprosthesis (stent) is used in
combination with a balloon catheter drug delivery system.
An endoprosthesis 50
is placed over the balloon catheter 51, and then coated with a noncomplexed
hydrogel coating 52. The drug 8, shown as circles, in aqueous solution is then
absorbed into the hydrogel coating 52. The balloon 51 and hydrogel and drug
coated endoprosthesis 50 are slid until they reach the region of the occlusion
53 in the vessel 54. This is shown in FIG. 4. An enlargement of the drug and
hydrogel polymer coated endoprosthesis 50 is shown in FIGS. 4a and 4b
(thickness of coating 52 is greatly exaggerated). After the balloon 51 and
hydrogel and drug coated endoprosthesis 50 have been positioned inside the
vessel 54, the endoprosthesis 50 is radially expanded by the admission of
pressure to the balloon 51 and compressed against the vessel wall 54 with the
result that occlusion 53 is compressed, and the vessel wall 54 surrounding it
undergoes a radial expansion. The pressure from inflating the balloon squeezes
the hydrogel 52, freely releasing the drug 8 into the tissue. The
endoprosthesis 50 is held in position in the expanded state as shown in FIG. 5.
The pressure is then released from the balloon and the catheter is withdrawn
from the vessel. FIG. 6 shows the drug 8 inside the compressed thrombus with
the endoprosthesis expanded and left in position, with the balloon catheter
being withdrawn from the lumen. It will be understood that only the
endoprosthesis may include the hydrogel polymer coating.

In the embodiments employing a hydrogel-coated stent, the hydrogel and drug are selected such that an initial high dosage of drug is delivered to adjacent tissue upon initial compression of the polymer and thereafter a slow, sustained time-release of drug remaining in the hydrogel polymer occurs. Preferred hydrogel-drug combinations are those that employ a binding of the drug, such as electrostatic binding, e.g., by using a polyacrylic acid hydrogel in combination with an ammonium cation and heparin. In this case, the coating continues to release drug after expansion of the stent and removal of the balloon catheter. The stent may be a balloon-expansible stent as described above or a self-expanding stent, e.g., of the type formed with super-elastic materials such as Nitinol.

Detailed Description Text - DETX (25):

Any of the embodiments discussed herein can be used with a protective sheath as described in FIGS. 2-2a. In addition, a heated balloon catheter may be used in all combinations of the embodiments above to enhance and control the rate of drug-solution delivery into tissue. Other compressible sponge-like polymers, e.g., non hydrogels which release drug solutions in response to pressure, might be used as described with respect to the embodiment of FIG. 1 et seq.

Claims Text - CLTX (2):

providing a catheter constructed for insertion into a vascular lumen having a catheter shaft and an expandable portion mounted on said catheter shaft, said expandable portion being expandable in response to controlled inflation pressure to fill the cross-section of the vascular lumen and engage the tissue or occlusive formation of said vascular lumen, at least a

portion of the
exterior surface of the expandable portion being defined by a coating of a
tenaciously adhered swellable hydrogel polymer, having said dose of said
aqueous-mobile drug incorporated therein said hydrogel polymer selected to
cause the coating to reach a characteristic swollen state of a thickness a
number of times thicker than the thickness of the coating in its dry state as a
result of absorption of aqueous fluid, and, when in said swollen state, said
coating having characteristic compressibility, in response to compressive
pressure within said expandable portion elevated above said inflation pressure,
to squeeze the coating against said tissue or occlusive formation sufficiently
to immediately, substantially, reduce the coating thickness, and force a
substantial portion of said dose of said aqueous-mobile drug into said tissue
or occlusive formation,

Claims Text - CLTX (4):
swelling said hydrogel polymer coating,

Claims Text - CLTX (6):
expanding said expandable portion to cause immediate delivery of said drug
by compression of said hydrogel polymer coating against the wall of said body
lumen or said occlusive formation for a brief interval, during which said dose
of said preselected drug is rapidly squeezed from said hydrogel coating and
delivered to said tissue;

Claims Text - CLTX (12):
5. The method of claim 6 including a binding of said drug and said hydrogel
polymer in a coating upon said stent for slow time release of drug remaining in
said hydrogel polymer on said stent after compression of

said hydrogel polymer
by said expansion.

Claims Text - CLTX (14):
7. The method of claim 6 wherein said stent and balloon both include said
swellable hydrogel polymer coating incorporating said drug.

Claims Text - CLTX (15):
8. The method of claim 1 further comprising positioning said expandable
portion at a point of occlusion in said vascular lumen and expanding said
expandable portion at pressures sufficient to simultaneously dilate said vessel
and deliver said drug by compression of said hydrogel polymer coating.

Claims Text - CLTX (19):
12. The method of claim 11 wherein said hydrogel polymer is selected from
the group consisting of polycarboxylic acids, cellulosic polymers, gelatin
polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl
alcohols, and polyethylene oxides.

Claims Text - CLTX (20):
13. The method of claim 12 wherein said hydrogel polymer is polyacrylic
acid.

Claims Text - CLTX (25):
at least a part of the exterior surface of the expandable portion being
defined by a coating of a tenaciously adhered swellable hydrogel polymer, and
incorporated within said hydrogel polymer, a preselected aqueous-mobile drug to
be delivered to said tissue or occlusive formation, said drug selected from the
groups of drugs that reduce vascular lumen occlusion problems caused by blood

clots or tissue cell proliferation,

Claims Text - CLTX (26):
said hydrogel polymer selected to cause the coating to reach a characteristic swollen state of a thickness a number of times thicker than the thickness of the coating in its dry state as a result of absorption of aqueous fluid, and, when in said swollen state, said coating having characteristic compressibility, in response t compressive pressure within said expandable portion elevated above said inflation pressure, to squeeze the coating against said tissue or occlusive formation sufficiently to immediately, substantially, reduce the coating thickness, and force a substantial portion of said aqueous-mobile drug into said tissue or occlusive formation, thereby to enable rapid administration of a desired dose of said drug into said tissue or occlusive formation.

Claims Text - CLTX (27):
17. The catheter of claim 16 wherein said catheter is a dilatation catheter sized, constructed and arranged for insertion in a stenosed vascular lumen, and said expandable portion is an inflatable dilatation balloon adapted for brief inflation at pressures in the range for effecting widening of said stenosed vascular lumen, said elevated compressive pressure being in a range effective to simultaneously cause, with said compression of said hydrogel a administration of said drug, widening of said vascular lumen.

Claims Text - CLTX (28):
18. The catheter of claims 17 or 16 wherein said hydrogel polymer is selected from the group consisting of polycarboxylic acids,

cellulosic
polymers, gelatin, polyvinylpyrrolidone, maleic anhydride
polymers, polyamides,
polyvinyl alcohols, and polyethylene oxides.

Claims Text - CLTX (29):
19. The catheter of claim 18 wherein said hydrogel
polymer is polyacrylic
acid.

Claims Text - CLTX (37):
27. The catheter of claim 17 or 26 wherein said
hydrogel polymer is
effective to release about 20% or more of said drug during
inflation in said
pressure range.

Claims Text - CLTX (39):
29. The catheter of claim 28 wherein the response
characteristic of said
hydrogel to said compressive pressure is effective to
deliver said dose of said
drug over a duration of about 10 minutes or less.

Claims Text - CLTX (40):
30. The catheter of claim 28 wherein said hydrogel
polymer coating is about
10 to 50 microns thick in the swelled, uncompressed state.

Claims Text - CLTX (42):
32. The catheter of claim 28 wherein the hydrogel
releases about 50% of the
drug upon compression.

Claims Text - CLTX (43):
33. The catheter of claim 28 wherein the drug is
precipitated into the
hydrogel.

Claims Text - CLTX (47):
37. The catheter of claim 36 including a binding of

said drug and hydrogel
polymer in a coating upon said stent for slow time release of drug remaining in
said hydrogel polymer on said stent after said compression of said hydrogel
polymer by said expansion.

Claims Text - CLTX (48):
38. The catheter of claim 37 wherein said hydrogel polymer coating on said
stent is a polyacrylic acid including an ammonium anion, said drug is heparin
and said binding is an electrostatic binding.

Claims Text - CLTX (50):
40. The catheter of claim 39 wherein said stent and balloon both include
said swellable hydrogel coating incorporating said drug.

Claims Text - CLTX (53):
43. The catheter of any one of claims 2, 16 or 35 wherein the response
characteristic of said hydrogel to said compressive pressure is effective to
deliver said dose of said drug over a duration of about 10 minutes or less.

Claims Text - CLTX (54):
44. The catheter of any one of claims 17, 16 or 35 wherein said hydrogel
polymer coating is about 10 to 50 microns thick in the swelled, uncompressed
state.

Claims Text - CLTX (57):
at least a portion of the exterior surface of the expandable balloon being
defined by a coating of a tenaciously adhered swellable hydrogel polymer having
said dose of said aqueous-mobile drug incorporated therein, said hydrogel
polymer selected to cause the coating to reach a characteristic swollen state

of a thickness a number of times thicker than the thickness of the coating in its dry state as a result of absorption of aqueous fluid, and, when in said swollen state, said coating having characteristic compressibility, in response to said compressive pressure within said expandable balloon elevated above said inflation pressure, to squeeze the coating against said tissue or occlusive formation sufficiently to immediately, substantially, reduce the coating thickness, and force a substantial portion of said dose of said aqueous-mobile drug into said tissue or occlusive formation, said hydrogel polymer coating further characterized by having the capacity to incorporate a predetermined substantial amount of aqueous fluid and said drug and by being swellable by a factor of about 6 or more from a dried state to have a thickness in the range of about 10 to 50 microns in the swelled state,

Claims Text - CLTX (58):

whereby rapid site specific release of a desired dose of about 20% or more of said aqueous-mobile drug from said hydrogel polymer coating is achieved during a brief interval of compression of said hydrogel polymer coating against the wall of the lumen when said expandable balloon is expanded in said pressure range.

Claims Text - CLTX (59):

46. The catheter of claim 45 wherein said hydrogel polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, and polyethylene oxides.

Claims Text - CLTX (60):

47. The catheter of claim 45 wherein said hydrogel polymer is polyacrylic acid.

Claims Text - CLTX (64):
51. The catheter of any one of claims 45, 16 or 35 or the method of claim 1 wherein the hydrogel releases about 50% of the drug upon compression.

Claims Text - CLTX (67):
54. The catheter or method of claim 50 wherein the hydrogel includes up to about 20-30 mg of aqueous drug solution.

Claims Text - CLTX (68):
55. The catheter of any one of claims 45, 16 or 35 or the method of claim 1 wherein the drug is precipitated into the hydrogel.

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Sahatjian et al.

US Reference Group - URGP (21):
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US-PAT-NO: 6626939

DOCUMENT-IDENTIFIER: US 6626939 B1

TITLE: Stent-graft with bioabsorbable structural support

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Brief Summary Text - BSTX (16):

In sum, the invention relates to a stent-graft including a bioabsorbable structural support including a tubular body having open ends, a sidewall structure having openings therein, and an inside and an outside surface and a permanent graft having an inside and outside surface. One of the bioabsorbable structural support or the permanent graft cooperates with the other and provides a coextensive portion wherein at least a part of the coextensive portion has a length of the bioabsorbable structural support and a length of the permanent graft bonded or interbraided together. The coextensive portion may be part or all of the longitudinal length of the stent-graft. The stent-graft may be adjustable between a nominal state and a radially-reduced state. The tubular body may further include a plurality of bioabsorbable elements formed in a generally elongated shape which is generally radially compressible and self-expandable. The stent-graft may provide an initial radial force when implanted in a body lumen and the bioabsorbable structure portion bioabsorbs over time in-vivo with an eventual resulting decrease in radial force to the vessel wall, and the permanent graft portion substantially remains in the body lumen. The structural support and the permanent graft may

be bonded by adhesive means and the adhesive means may be bioabsorbable. The adhesive means may occupy a proximal and a distal end portion but not a mid portion over the coextensive portion which the structural support and graft are coextensive one another. The bioabsorbable structural support may be made of at least one of poly (alpha-hydroxy acid), PGA, PLA, PLLA, PDLA, polycaprolactone, polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester, poly(amino acids), or combinations thereof and the graft may be made of at least one of PET, ePTFE, PCU, or PU. The elements may be substantially homogeneous in cross section and length. The graft may include a plurality of interwoven fibers, mono-filaments, multi-filaments, or yarns. The graft may be a film, sheet, or tube. The graft may form a composite wall with body tissue in the body lumen. The stent-graft may be permeated with body tissue and may provide structural support to a body lumen for less than about 3 years. The graft may be disposed on at least one of the inside and outside surface of the structural support. The graft and the filaments may be interbraided. The bioabsorbable structural support may be annealed.

Claims Text - CLTX (11):

11. The stent-graft of claim 1 wherein: the filaments are made of a bioabsorbable material selected from the group consisting of: poly (alpha-hydroxy acid), PGA, PLA, PLLA, PDLA, polycaprolactone, polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly (hydroxybutyrate), polyanhydride, polyphosphoester,

poly (amino acids), and combinations thereof, and the graft is made of a
polymer selected from the group consisting of: PET, ePTFE, PCU, and PU.

US006280411B1

(12) **United States Patent**
Lennox

(10) **Patent No.: US 6,280,411 B1**
(45) **Date of Patent: Aug. 28, 2001**

(54) **LOCALIZED DELIVERY OF DRUG AGENTS**

(75) Inventor: **Charles D. Lennox**, Hudsom, NH (US)

(73) Assignee: **Scimed Life Systems, Inc.**, Maple Grove, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/080,237**

(22) Filed: **May 18, 1998**

(51) **Int. Cl.**[7] **A61M 29/00**

(52) **U.S. Cl.** **604/103.05**; 604/96.01; 604/103.01; 604/103.02; 604/103.05; 604/103.11; 604/103.12; 606/192; 606/194; 623/1.39; 623/1.42

(58) **Field of Search** 604/96, 101, 265, 604/103, 104, 500, 507–509, 96.01, 101.01, 101.02, 103.01, 103.02, 103.05, 103.06, 103.11–103.12, 915, 917, 103.09; 606/108, 192, 194, 198; 623/1.1, 1.11, 1.15, 1.18, 1.2, 1.23, 1.39, 1.4, 1.42, 1.43, 1.44–1.46

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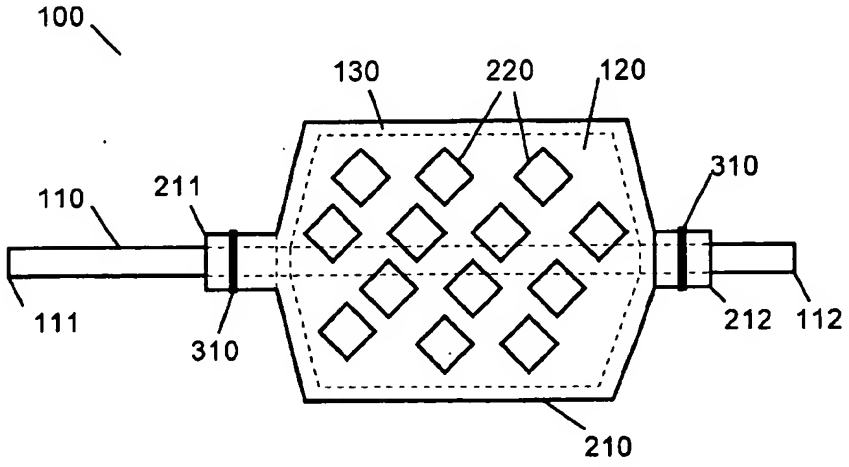
Primary Examiner—Richard K. Seidel
Assistant Examiner—LoAn H. Thanh
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

Medical devices including a substrate that are expandable from a compressed state to an expanded state; a coating on the substrate, the coating having a drug agent incorporated therein; and a sheath over the coating. The sheath is expandable from a compressed state to an expanded state and has at least one perforation therein. The medical devices are configured such that when the substrate is in a compressed state, the sheath is also in a compressed state and the perforation is substantially closed. When the substrate is in an expanded state, the sheath is also in an expanded state and the perforation is substantially open. The invention also includes a method of using the medical devices for the controlled, localized delivery of a drug agent to a target location within a mammalian body.

25 Claims, 3 Drawing Sheets



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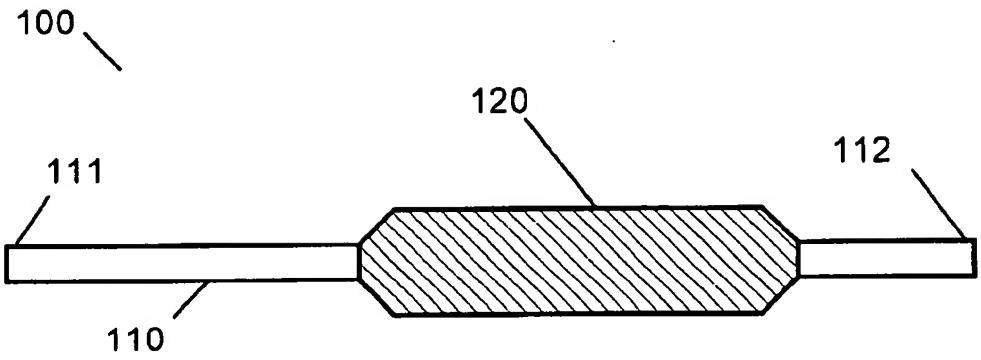

Fig. 1

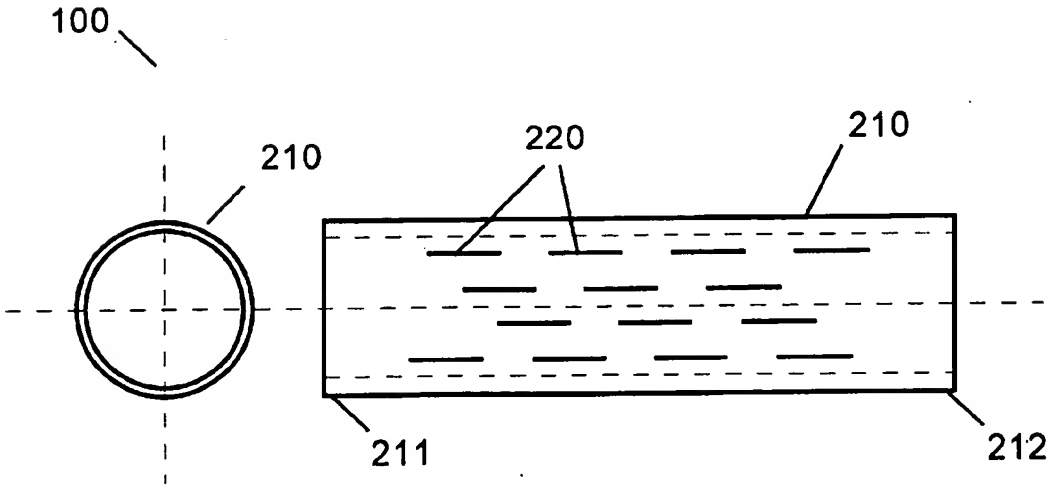

Fig. 2

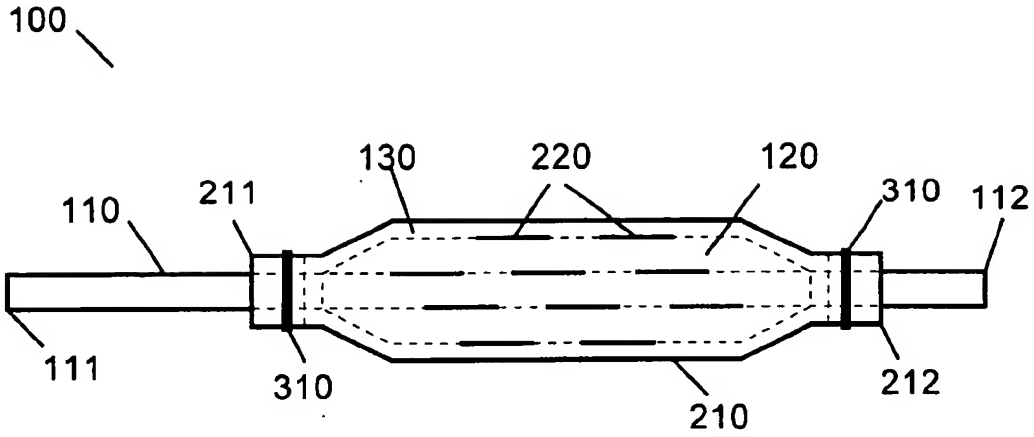
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Fig. 3

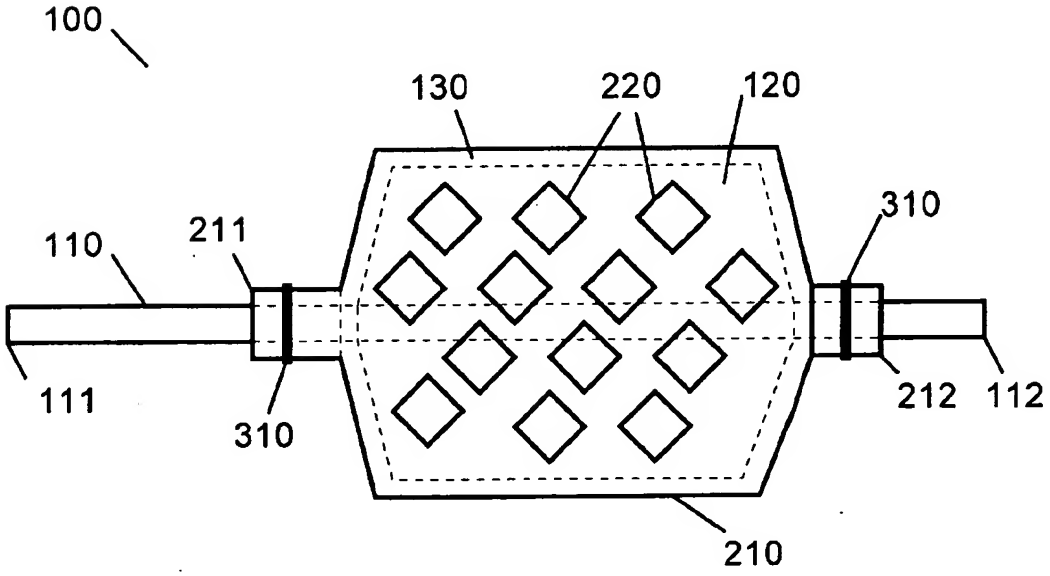
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Fig. 4

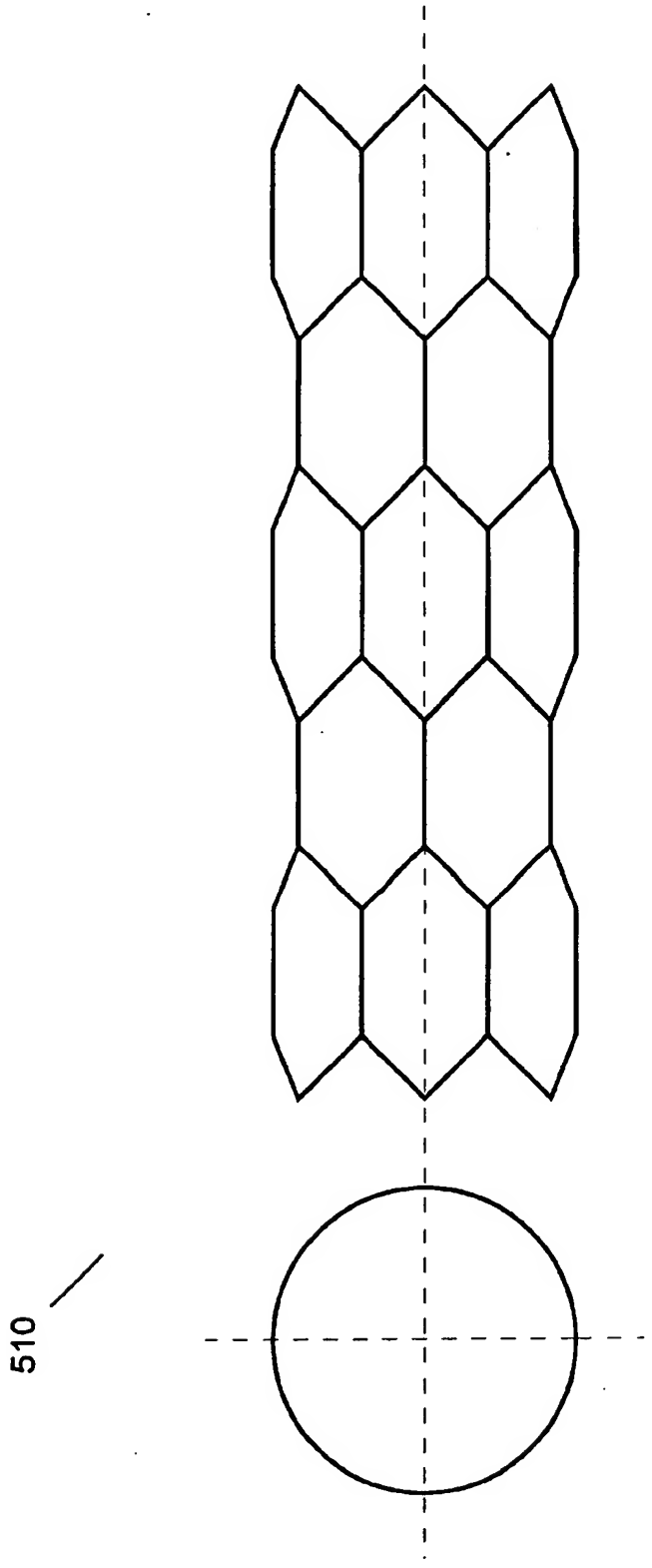

Fig. 5

LOCALIZED DELIVERY OF DRUG AGENTS

FIELD OF THE INVENTION

The present invention relates to methods and devices for the controlled, localized delivery of drug agents within a mammalian body.

BACKGROUND OF THE INVENTION

The systemic administration of drug agents, such as by transoral or intravenous means, treats the body as a whole even though the disease to be treated may be localized. In such a case, systemic administration may not be desirable because the drug agents may have unwanted effects on parts of the body which are not to be treated, or because treatment of the diseased part of the body requires a high concentration of drug agent that may not be achievable by systemic administration.

It is therefore often desirable to administer drug agents at localized sites within the body. Common examples include cases of localized disease (e.g., heart disease) or occluded body lumens. Various methods have been proposed for such localized drug administration. For example, U.S. Pat. No. 5,304,121, which is incorporated herein by reference, discloses a method of delivering water-soluble drugs to tissue at desired locations of a body lumen wall. The method generally includes the steps of impregnating a hydrogel polymer on a balloon catheter with an aqueous drug solution, inserting the catheter into a blood vessel to a desired location, and expanding the catheter balloon against the surrounding tissue to allow the release of the drug.

One of the potential drawbacks to conventional drug delivery techniques using drug-impregnated polymer coatings on balloon catheters is the possible premature diffusion of the drug out of the coating during delivery into the body. Two solutions to this problem have been proposed: the use of a removable sheath over the polymer coating, and the use of a dissolvable or meltable temporary coating over the polymer coating to protect and retain the drug agent in the coating prior to a time of desired administration at a target location. The sheath approach, however, adds considerable profile to the balloon catheter device, making access to small body lumens difficult or impracticable. Furthermore, the use of a temporary protective coating over a drug-impregnated polymer coating may place undesirable time constraints on the drug delivery procedure. Moreover, it is difficult to identify or develop temporary coatings that permit the release of the drug in a consistent and predictable manner.

In view of the potential drawbacks to conventional drug delivery techniques, there exists a need for a device and method for the controlled, localized delivery of drug agents to target locations within a mammalian body while avoiding the premature release of drug agent during delivery.

SUMMARY OF THE INVENTION

In one aspect, the present invention includes a medical device comprising a substrate that is expandable from a compressed state to an expanded state; a coating on the substrate and having a drug agent incorporated therein; and a sheath over the coating, the sheath being expandable from a compressed state to an expanded state and having at least one perforation therein. The medical device is configured such that when the substrate is in a compressed state, the sheath is likewise in a compressed state and the at least one perforation is substantially closed such that the drug agent does not pass through the at least one perforation. Moreover, when the substrate is in an expanded state, the sheath is likewise in an expanded state and the at least one perforation substantially opens such that the drug agent passes through the perforation.

In another aspect, the present invention includes a method for the localized delivery of drug agent to a target location within a mammalian body. The method comprises the steps of providing the medical device of the present invention; incorporating the drug agent into the coating of the device; delivering the medical device to the target location while the sheath is in a compressed state and the at least one perforation is substantially closed; and expanding the substrate to thereby expand the sheath such that the at least one perforation is substantially open. When the at least one perforation is substantially open, the drug agent moves from the coating through the perforation and into the body.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows an expandable catheter in accordance with an embodiment of the present invention.

FIG. **2** shows side and end views of an expandable sheath in accordance with an embodiment of the present invention.

FIG. **3** shows an expandable catheter and overlying expandable sheath in a compressed state, in accordance with an embodiment of the present invention.

FIG. **4** shows an expandable catheter and overlying expandable sheath in an expanded state, in accordance with an embodiment of the present invention.

FIG. **5** shows side and end views of a stent used in an embodiment of the present invention.

DETAILED DESCRIPTION

The present invention provides medical devices and methods for the controlled, localized delivery of drug agents to target locations within a mammalian body while avoiding the premature release of drug agent during delivery. The medical devices of the present invention have a simple construction, provide a minimal cross-sectional profile, and allow for the easy and reproducible loading of drug agents.

The medical device of the present invention includes any one of a number of medical devices that are applicable to the localized delivery of drug agents to within the body. When an expandable catheter is chosen as the medical device of the present invention, the expandable portion is preferably a balloon as described with specific reference to FIGS. **1–4**. In this embodiment, the medical device **100** comprises an expandable catheter **110** having proximal and distal ends **111, 112**. Mounted towards the distal end **112** of the catheter **110** is an expandable portion **120**. The expandable portion **120** is a balloon, and more preferably, a perfusion balloon, as known in the art. Such balloon catheters are conventionally used for medical procedures such as, for example, angioplasty or the placement of stents to within body lumens such as coronary arteries.

The expandable portion **120** of catheter **110** is coated with a polymer for holding the drug agent during delivery into the body. The polymer coating **130** is preferably capable of absorbing a substantial amount of drug solution. The polymer coating **130** is placed onto the expandable portion **120** by any suitable mean such as, for example, immersing the expandable portion **120** into the polymer or a solution thereof, or spraying the polymer or solution thereof onto the expandable portion **120**. The polymer is typically applied to a thickness of about 1 to 10 microns, preferably about 2 to 5 microns. Very thin polymer coatings, e.g., of about 0.2–0.3

microns and much thicker coatings, e.g., more than 10 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coating onto the expandable portion **120** of catheter **110**. Such multiple layers can be of the same or different polymer materials.

The polymer coating **130** comprises any polymeric material capable of absorbing or otherwise holding the drug agent to be delivered. The polymeric material is, for example, hydrophilic or hydrophobic, and is preferably selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. The preferred polymer is polyacrylic acid, as described in U.S. Pat. No. 5,091,205, the disclosure of which is incorporated herein by reference. U.S. Pat. No. 5,091,205 describes medical devices coated with one or more polyisocyanates such that the devices become instantly lubricious when exposed to body fluids.

The medical device **100** includes an expandable sheath **210** (FIG. **2**), which is sized to fit over the polymer-coated expandable portion **120** of the catheter **110**. The sheath **210** comprises an elastic and resilient material such that it substantially conforms to the shape of the expandable portion **120** and expands and contracts with the expandable portion **120**. In a preferred embodiment, the sheath **210** is biased towards a compressed state to hold the expandable portion **120** in a compressed state when it is not expanded, thus minimizing the profile of the medical device **100**. Examples of materials used for the construction of the sheath **210** include metallic materials such as nitinol and stainless steel, and polymeric materials such as ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers, silicone rubber, SILASTIC™, aliphatic polyesters, and mixtures and copolymers thereof.

In the embodiment shown in FIG. **2**, the sheath is a cylindrical tube having at least one perforation **220** therein. The sheath **210** is placed over the polymer-coated expandable portion **120** of the catheter **110** while in a deflated state as shown in FIG. **3**. The proximal and distal ends **211**, **212** of the sheath **210** are preferably attached to the catheter **110** such that the expandable portion **120** is completely covered by the sheath **210**. The sheath **210** is attached to the catheter **110** by any suitable means, such as by adhesive materials and/or by winding a filament **310** (e.g., suture, etc.) around its proximal and distal ends **211**, **212**. The sheath **210** is of minimal thickness so to minimize the profile of the medical device **100**. The preferred thickness of the sheath **210** is approximately 5 mils or less.

As shown in FIG. **3**, the perforation(s) in the sheath **210** is (are) preferably longitudinal slits. While it is within the scope of the invention for the sheath **210** to have a single perforation, it is preferred that the sheath **210** contain multiple perforations in the shape of longitudinal slits arranged in a staggered pattern. In one embodiment, the sheath **210** contains multiple longitudinally-oriented perforations which measure approximately 0.75 cm in length, and are spaced approximately 0.25 cm apart in a longitudinal direction and approximately 15° apart in a radial direction.

The medical device **100** is delivered into the body while the expandable portion **120** is in a deflated shape as shown in FIG. **3**. As such, the sheath **210** is in a compressed state and the perforations **220** are substantially closed such that the drug agent in the polymer coating **130** does not pass through the perforations **220**. Delivery of the medical device **100** into the body and to a target location occurs, for example, through a body lumen (e.g., coronary arteries, portal vein, ileofemoral vein, etc.) by torquing or other known techniques.

Once the medical device **100** is positioned to a target location within the body, the expandable portion **120** is expanded as shown in FIG. **4** to facilitate the release of drug agent from the polymer coating **130**. The expandable sleeve **210** is constructed so that it will not rupture when the underlying expandable portion **120** of the catheter **110** is fully expanded. When the expandable portion **120** is in an expanded state, the sheath **210** is also in an expanded state and the perforations **220** become substantially open such that the drug agent in the polymer coating **130** passes through the perforations **220**. The drug agent is released from the polymer coating **130** by any suitable mechanism, such as by diffusion or pressure-enhanced release.

The drug agents used in the present invention include, for example, pharmaceutically active compounds, proteins, oligonucleotides, genes, DNA compacting agents, gene/vector systems (i.e., anything that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, DNA, cDNA, RNA, antisense DNA or RNA), and viral, liposomes and cationic polymers that are selected from a number of types depending on the desired application. For example, biologically active solutes include anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone); anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine; antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin, protaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides; vascular cell growth promotors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional activators, and translational promotors; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogeneus vascoactive mechanisms. These and other compounds are added to the polymer coating using similar methods and routinely tested as set forth in the specification. Any modifications are routinely made by one skilled in the art.

Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell. Examples of therapeutic polynucleotides include anti-sense DNA and RNA; DNA

coding for an anti-sense RNA; or DNA coding for tRNA or rRNA to replace defective or deficient endogenous molecules. The polynucleotides of the invention can also code for therapeutic polypeptides. A polypeptide is understood to be any translation product of a polynucleotide regardless of size, and whether glycosylated or not. Therapeutic polypeptides include as a primary example, those polypeptides that can compensate for defective or deficient species in an animal, or those that act through toxic effects to limit or remove harmful cells from the body. In addition, the polypeptides or proteins that can be incorporated into the polymer coating **130**, or whose DNA can be incorporated, include without limitation, angiogenic factors including acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived enotheial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CD inhibitors; thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, including agents for treating malignancies. Still other useful factors, which can be provided as polypeptides or as DNA encoding these polypeptides, include the family of bone morphogenic proteins ("BMP's"). The known proteins include BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

The drug agent is introduced into the polymer coating **130** by any suitable method. For example, the drug agent is placed in solution, which is thereafter applied to the polymer coating **130** by any suitable means, including dipping the polymer coating **130** into the drug solution or by applying the solution onto the coating **130** such as by pipet or spraying. In the former method, the amount of drug loading is controlled by regulating the time the polymer is immersed in the drug solution, the extent of polymer cross-linking, the concentration of the drug in the solution and/or the amount of polymer coating. In another embodiment of the invention, the drug is incorporated directly into the polymer prior to the application of the polymer as a coating onto a medical device. The drug agent can be applied to the polymer coating **130** either before or after the sheath **210** is placed over the coating **130**. For example, if applied after the sheath **210** is placed over the coating **130**, the expandable portion **120** is expanded to thereby open the perforations **220** in the sheath **210** as shown in FIG. **4**. The drug agent is thereafter incorporated into the polymer coating **130** through the open perforations **220** by any suitable means such as, for example, dipping the medical device **100** into a solution of drug agent. The method of incorporating the drug agent into the coating **130** through the open perforations **220** is generally preferred, especially where the polymer coating **130** is loaded multiple times with the same or different drug agents.

The release profile of the drug from the polymer coating **130** is determined by many factors including the drug solubility, the thickness and porosity of the polymer coating, and the number and size of perforations **220** in the sleeve **210**. When an expandable member such as a balloon catheter is used to administer the drug, pressure can be used to increase the rate of drug transfer to the tissue. An increase in pressure increases the diameter of the balloon and therefore the diameter of the surrounding tissue (if contacted by the balloon), thereby increasing the surface area for drug transfer. The amount of drug that is delivered per unit time is therefore increased. An increase in the rate of drug release from the polymer coating **130** is also accomplished by increasing both the number and size of perforations **220** in the sleeve **210**.

During drug administration, a substantial amount of the drug agent contained in the polymer coating **130** is diffused into the affected area. The inflation pressure needed to expand the expandable portion **120** of catheter **110** is typically in the range of about 1 to 20 atm. When the expandable portion **120** comprises a balloon, it is formed of any suitable material such as vinyl polymers such as polyethylene; polyesters such as polyethylene terephthalate; polyamides such as nylon; polyolefins and copolymers thereof (e.g., Selar, Pebax, Surlyn, Hytrel, etc.). The balloon is optionally a perfusion balloon, which allows blood to perfuse the catheter to prevent ischemia during delivery. A perfusion balloon is particularly preferred for long arterial delivery times and when the delivery drug is only very slightly soluble in water.

In one embodiment, the medical device **100** of the present invention includes a stent **510** (FIG. **5**) for placement in a body lumen. The present invention can thus be used for the dual purpose of localized drug delivery and stent placement. As known in the art, stents are tubular support structures that are implanted inside tubular organs, blood vessels or other tubular body lumens. The stent used with the present invention is of any suitable design, and is either self-expanding or balloon-expandable. The stent is made of any suitable metallic (e.g., stainless steel, nitinol, tantalum, etc.), polymeric (e.g., polyethylene terephthalate, polyacetal, polylactic acid, polyethylene oxide—polybutylene terephthalate copolymer, etc.) or biodegradable material. The stent **510** is preferably metallic and configured in a mesh design, as shown in FIG. **5**. When used with the present invention, the stent **510** is placed over the sheath **210** when each of the expandable portion **120**, the sheath **210**, and the stent **510** are in a compressed state. The medical device **100** is thereafter delivered to a target location within the body, as previously described. In this embodiment, the target location is situated within a body lumen. When the expandable portion **120** is expanded to release the drug agent from the polymer coating **130**, the stent **510** is likewise expanded. After the drug agent has been released from the polymer coating **130**, the expandable portion **120** is compressed or deflated such that the sheath **210** is compressed with the expandable portion **120**. The stent **510**, however, remains in its expanded state within the body lumen.

The medical device of the present invention is optionally used to accomplish electroporation, in which short pulses of high electric fields are applied to a target location in the body to thereby cause cell membranes to become porous so that drug agents can diffuse therein. Any suitable modification of the medical device is made to facilitate electroporation as is known in the art, such as, for example, the inclusion of electrodes. The medical device of the present invention may also be modified, as is known in the art, for accomplishing iontophoresis in which a current is applied at the target location to promote the delivery of ionic drug agents.

The present invention provides a system and method for the localized delivery of drug agent to target locations within a mammalian body. Although the present invention has been

described with respect to several exemplary embodiments, there are many other variations of the above-described embodiments which will be apparent to those skilled in the art, even where elements have not explicitly been designated as exemplary. It is understood that these modifications are within the teaching of the present invention, which is to be limited only by the claims appended hereto.

What is claimed is:

1. A medical device, comprising:

a substrate that is expandable from a compressed state to an expanded state;

a coating on said substrate, said coating having a drug agent incorporated therein, wherein said drug agent is incorporated in said coating prior to delivering said medical device to a target location within a mammalian body; and

an elastic sheath over said coating, said elastic sheath being expandable from a compressed state to an expanded state and having at least one perforation therein;

wherein when said substrate is in a compressed state, said elastic sheath is in a compressed state and said at least one perforation is substantially closed such that said drug agent does not pass through said at least one perforation; and

wherein when said substrate is in an expanded state, said elastic sheath is in an expanded state and said at least one perforation is substantially open such that said drug agent passes through said at least one perforation.

2. The device of claim 1, wherein said substrate comprises at least part of a ballon portion of a ballon catheter.

3. The device of claim 2, wherein said elastic sheath is tubular and surrounds said balloon portion of said balloon catheter, said tubular elastic sheath having proximal and distal ends.

4. The device of claim 3, wherein said proximal and distal ends of said elastic sheath are attached to said balloon catheter such that said balloon portion is completely covered by said elastic sheath.

5. The device of claim 4, wherein said proximal and distal ends of said elastic sheath are attached to said balloon catheter by an adhesive.

6. The device of claim 4, further comprising a filament around said proximal and distal ends of said elastic sheath.

7. The device of claim 1, wherein said at least one perforation is in the shape of a longitudinal slit.

8. The device of claim 7, wherein said elastic sheath comprises a plurality of perforations arranged in a staggered pattern.

9. The device of claim 1, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

10. The device of claim 1, wherein said drug agent is selected from the group consisting of pharmaceutically active compounds, proteins, oligonucleotides, DNA compacting agents, recombinant nucleic acids, gene/vector systems, and nucleic acids.

11. The device of claim 1, wherein said elastic sheath comprises a material selected from the group consisting of ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers, aliphatic polyesters, and mixtures and copolymers thereof; and nitinol and stainless steel.

12. A method for the localized delivery of a drug agent to a target location within a mammalian body, comprising the steps of:

providing a medical device comprising:

a substrate that is expandable from a compressed state to an expanded state;

a coating on said substrate; and

an elastic sheath over said coating, said elastic sheath being expandable from a compressed state to an expanded state and having at least one perforation therein;

wherein when said substrate is in a compressed state, said elastic sheath is in a compressed state and said at least one perforation is substantially closed; and

wherein when said substrate is in an expanded state, said elastic sheath is in an expanded state and said at least one perforation in said elastic sheath is substantially open;

incorporating said drug agent into said coating;

delivering said medical device having said drug agent incorporated into said coating to said target location while said elastic sheath is in a compressed state and said at least one perforation is substantially closed; and

expanding said substrate to thereby expand said elastic sheath to an expanded state such that said at least one perforation is substantially open, whereby the drug agent passes through said at least one perforation.

13. The method of claim 12, wherein said substrate comprises at least part of a balloon portion of a balloon catheter.

14. The method of claim 13, wherein said elastic sheath is tubular and surrounds said balloon portion of said balloon catheter, said tubular elastic sheath having proximal and distal ends.

15. The method of claim 14, wherein said proximal and distal ends of said elastic sheath are attached to said balloon catheter such that said balloon portion is completely covered by said elastic sheath.

16. The method of claim 12, wherein said at least one perforation is in the shape of a longitudinal slit.

17. The method of claim 16, wherein said at least one perforation comprises a plurality of perforations arranged in a staggered pattern.

18. The method of claim 12, wherein said step of incorporating the drug agent into said coating comprises the steps of:

expanding said substrate to thereby expand said elastic sheath such that said at least one perforation is substantially open;

exposing said drug agent to said coating through said at least one perforation while said at least one perforation is substantially open; and

compressing said substrate to thereby compress said elastic sheath such that said at least one perforation is substantially closed.

19. The method of claim 18, wherein said drug agent is exposed to said coating by immersing at least part of said medical device into a solution comprising said drug agent.

20. The method of claim 12, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides,

glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

21. The method of claim **12**, wherein said drug agent is selected from the group consisting of pharmaceutically active compounds, proteins, oligonucleotides, genes, DNA compacting agents, gene/vector systems, and nucleic acids.

22. The method of claim **12**, wherein said elastic sheath comprises a material selected from the group consisting of ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers, aliphatic polyesters, and mixtures and copolymers thereof; and nitinol and stainless steel.

23. The method of claim **12**, wherein said medical device comprises an electroporation catheter.

24. The method of claim **12**, wherein said medical device comprises an iontophoresis catheter.

25. A medical device, comprising:

a catheter comprising a balloon portion that is expandable from a compressed state to an expanded state;

a polymer coating on said balloon portion, said coating having a drug agent incorporated therein, wherein said drug agent is incorporated in said coating prior to delivering said medical device to a target location within a mammalian body; and

a tubular elastic sheath over said coating, said elastic sheath being expandable from a compressed state to an expanded state and having a plurality of perforations therein, said perforations being arranged in a staggered pattern; wherein

the proximal and distal ends of said elastic sheath are attached to said catheter such that said balloon portion is completely covered by said elastic sheath;

when said balloon portion is in a compressed state, said elastic sheath is in a compressed state and said perforations are substantially closed such that said drug agent does not pass through said perforations; and

when said balloon portion is in an expanded state, said elastic sheath is in an expanded state and said perforations are substantially open such that said drug agent passes through said perforations.

* * * * *

US006309380B1

(12) **United States Patent**
Larson et al.

(10) **Patent No.: US 6,309,380 B1**
(45) **Date of Patent: Oct. 30, 2001**

(54) **DRUG DELIVERY VIA CONFORMAL FILM**

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(58) **Field of Search** ..... 604/28, 264, 265, 604/174, 175, 96 A, 891.1, 500, 502; 128/898; 606/192, 194; 424/422–423; 427/2.1

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(57) **ABSTRACT**

A drug delivery conformal film system according to the present invention is adapted to be compounded and applied, by medical personnel at the point of use, to a medical device such as a cardiovascular and urology stent, pacemaker, vascular graft, suture ring of mechanical heart valve, implantable infusion port, implantable drug delivery pump, orthopedic hardware and appliance, and, neurological stimulating device. The drug delivery conformal film consists of one of three in vivo biocompatible; biodegradable, bioerodable or bioabsorbable embodiments: (1) cross-linked sodium alginate, (2) UV photo-active polymer, or, (3) hydrogels. An implantable medical device such as the stent or suture ring of a mechanical artificial heart valve is coated with an in vivo biocompatible; biodegradable or bioerodable or bioabsorbable solution comprising a polymer and containing a drug, the solution is cross-linked or cured to form a film on the device immediately prior to placement in the body. When the coated device is introduced into the body, the drug contained in the coating is released in a local region. The invention provides a point of use in vivo drug delivery system whereby the drug and its concentration can be selected by medical personnel immediately prior to implantation of the medical device.

17 Claims, No Drawings

DRUG DELIVERY VIA CONFORMAL FILM

FIELD OF THE INVENTION

The present invention relates to the local delivery of drugs in vivo into the cardiovascular system and other body regions. In particular, the present invention is directed to the local delivery of drugs by applying a coating of a bioabsorbable/biodegradable or inert, in vivo biocompatible conformal film, to an implantable medical device.

BACKGROUND OF THE INVENTION

Angioplasty is a procedure that involves placing and inflating a balloon catheter in the blood vessel in the area of blockage, which breaks up the accumulated plaque and opens the vessel. While this technique works well in the short term, current literature indicates that 30 to 50% of all angioplasty operations performed will need follow-up treatment within six months. This is due to incomplete plaque removal and the formation of scar tissue as a result of irritation of the blood vessel, known as restenosis. Restenosis results in significant morbidity and mortality and often necessitates further interventions such as repeat angioplasty , coronary bypass, laser surgery or local drug delivery. There has been a focused effort in the health-care industry over the last few years to combat restenosis because repeat angioplasty or surgery is expensive, inconvenient, and potentially life threatening.

Limitations of angioplasty long-term success include abrupt closure (4.4–8.3%) and restenosis (chronic reclosure 30–50%) of the vessel—both of which are associated with excessive vascular injury.

Intravascular stenting (the placement of a supporting structure within a blood vessel) has demonstrated moderate success in addressing these issues. These devices provide structural support to keep the vessel walls from closing and minimize the problem of arterial blockage caused by plaque falling in to the vessel after inflation.

Stents have been made using materials of varied composition. U.S. Pat. No. 4,886,062 to Wiktor describes a stent made from low memory metal such as a copper alloy, titanium, or gold. Current stent designs tend to be thrombogenic (causing clot formation) and immunologically stimulating (causing cell formation). Current metal stent designs will not eliminate the restenosis problem. If restenosis should recur, follow-up treatments such as laser surgery or localized drug delivery using other angioplasty devices may be required. A stent alone can not restrict hyperplasia of smooth muscle cells, nor can it prevent restenosis or thrombus. Local delivery of antithrombogenic drugs and those capable of restricting hyperplasia of smooth muscle cells is desirable.

Drugs have been incorporated on or in a catheter or stent during the manufacturing design to provide local delivery of drugs to address restenosis, thrombus, and coagulation. U.S. Pat. No. 4,994,033 to Shockey et al.; U.S. Pat. No. 5,674,192 to Sahatjian et al. and U.S. Pat. No. 5,545,208 to Wolff et al. disclose catheters comprising absorbable/biodegradable polymers or hydrogels containing the desired dosage of a drug . Stents incorporating drug delivery may be found, for example, in U.S. Pat. No. 5,766,710 to Tumiund et al.; U.S. Pat. No. 5,769,883 to Buscemi et al.; U.S. Pat. No. 5,605,696 to Eury et al.; U.S. Pat. No. 5,500,013 to Buscemi et al.; U.S. Pat. No. 5,551,954 to Buscemi et al. and U.S. Pat. No. 5,443,458 to Eury.

When drugs or biological modifiers are applied in conjunction with the manufacture of the device, there are several problems, for example:

1. sterilization: heat or ionizing radiation alters the composition of many drugs and biological modifiers;
2. the presence of a drug imposes a shorter shelf life independent of the implantable medical device, and could require special storage (i.e. refrigeration);
3. the drug dosage is not variable for specific patient needs; and,
4. a large inventory of devices is required to provide a range of drugs and therapies.

It is an object of the present invention to provide a drug delivery system that overcomes the deficiencies associated with the application of drugs in conjunction with the manufacture of the device.

It is a further object of the present invention to provide a procedure where the drug is applied to the device at the point of use of the device.

SUMMARY OF THE INVENTION

The present invention is directed to a method of producing an implantable drug-deliverable medical device. The method comprises providing an implantable medical device, coating the device with an in vivo biocompatible and biodegradable or bioabsorbable or bioerodable liquid or gel solution containing a polymer with the solution comprising a desired dosage amount of one or more predetermined drugs. The solution is converted to a film adhering to the medical device thereby forming the implantable drug-deliverable medical device.

The present invention is also directed to a drug delivery conformal film system adapted to be applied by medical personnel at the point of use, to an implantable medical device such as cardiovascular and urology stents, pacemakers, vascular grafts, suture rings of mechanical heart valves, implantable injection or infusion ports, implantable drug delivery pumps, orthopedic hardware and appliances, and, neurological stimulating devices. The drug delivery conformal film comprises one of three in vivo biocompatible; biodegradable, bio-erodable or bio-inert embodiments: (1) cross-linked sodium alginate, (2) UV photo-active polymer, or, (3) hydrogels. A stent or other implantable medical device such as the suture ring of a mechanical artificial heart valve is coated with this biodegradable, bio-erodable or bio-inert material containing a drug, cross-linked or cured, or otherwise treated to form a film, immediately prior to placement in the body. When the film-coated device is introduced into the body, the drug contained in the film coating is released in a local region. The invention provides a point of use in vivo drug delivery system whereby the drug and its concentration can be selected by medical personnel immediately prior to implantation of the medical device.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention will now be discussed in detail with reference to the preferred embodiments. Unless otherwise stated, all percentages represent weight percent.

Drugs or other biologically active materials incorporated into the drug delivery conformal film system of the present invention are intended to perform a variety of functions, including, but not limited to: anti-clotting or anti-platelet formation, and the prevention of smooth muscle cell growth on the vessel wall. Drugs anticipated for delivery include antibiotics, anticoagulants, tissue generation factor, and angiogenesis drugs. Drugs also include, but are not limited

to, anti-thrombogenic drugs (heparin, PPACK, enoxaprin, aspirin, coumadin, hirudin, TPA, urokinase, and streptokinase), anti-proliferative drugs (monoclonal antibodies, heparin, angiopeptin, enxoaprin, methotrexate, cisplatin, flourouracil, Adriamycin), antimetabolites, thromboxane inhibitors, non- steroidal and steroidal anti-inflammatory drugs, Beta and Calcium channel blockers, genetic materials (including DNA and RNA fragments), and bioactive materials (such as fibronectin, laminin, elastin, collagen, and intergrins).

As stated previously, the drug delivery conformal film of the present invention comprises one of three in vivo biocompatible; biodegradable, bio-erodable or bio-inert embodiments: (1) cross-linked sodium alginate, (2) UV photo-active polymer, or, (3) hydrogels, for example, thermal irreversible hydrogels. Of these embodiments, cross-linked sodium alginate is preferred.

Sodium alginate is preferred because of its biocompatibility and in vivo biodegradability, and cross-linking film forming properties. A sterile and low endotoxin form of sodium alginate has recently become available under product number K8P569 from Monsanto, 800 N. Lindbargh Blvd. St. Louis, Mo., or under product number UP MVG from Pro Nova, Strandveien 18, N-1324 Lysaker, Norway. Very low endotoxin levels can be obtained in alginates by use of a highly specialized purification process. Alginates in a water gel form have the unique ability to form elastic films by reaction with calcium salts and/or magnesium salts. Once cross-linked, these films retain their shape and resist stress.

The preferred embodiment of the present invention is a medical release drug delivery conformal film system comprised of sterile, low endotoxin sodium alginate and sterile low-pyrogen water which uses a solution of calcium chloride to achieve gelation through cross-linking. The sodium alginates selected for this invention have a Mannuronic acid content of approximately 58 to 62% and a Guluronic acid content of approximately 42 to 38%. The alginate films thus produced have known and acceptable long-term biocompatibility and biodegradability in vivo and are manufactured in such a manner and form that renders the film sterile and biocompatible with human tissue, organs and body fluids. Sodium alginate in purified form, such as Monsanto part number K8P569 and ProNova part number UP MVG as a solution in water containing acceptably low levels of pyrogens is the preferred composition that demonstrates the desired in vivo biocompatibility and known in vivo biodegradability.

Alginates, such as sodium alginate, form aqueous solutions in either liquid or gel form. The addition of increasing amounts of non-aqueous water-miscible solvents (i.e., glycols) to an alginate solution increases the solubility of non-water-soluble compounds. As the alginate solution in this invention is intended to serve as a drug delivery film, non-water soluble drugs can be added to an alginate solution prepared with up to 10% propylene glycol, or other biocompatible solvents, substituted for water. Alternatively, water and the particular glycol may be mixed prior to the addition of the alginate. Furthermore, the drug may be added to the water/glycol mixture prior to the addition of the alginate.

Sodium alginates gel by cross-linking between a pH range of 3 to 5. Calcium chloride has been selected for its low pH and in vivo biocompatible characteristics to cross-link the algin gel creating a strong film. Alginates, when cross-linked with calcium chloride form a biodegradable/bioabsorbable film that is lubricious and thus provides a lubricating coating. This lubricious coating can assist in the insertion of the medical device into the human body.

Sodium alginate used in the embodiments of this invention may also include Monsanto Keltone HVCR. A formulation was prepared from the HVCR grade that represents the mannuronic acid and guluronic acid content that will produce suitable solutions of algin and is similar in characterizations to Monsanto part number K8P569 and ProNova part number UP MVG which is the most preferred alginate polymer of the invention. This solution has an acceptable viscosity, film forming rheology and film mechanical properties, and produces an in vivo biocompatible solution and film.

The alginate solution can be used to coat an implantable medical device, at its point of use, whereby the high viscosity alginate solution, to which a drug has been added, is rendered into a film by dipping the coated device into calcium chloride. To restrict the film to the exterior and perforations of a device, the internal diameter of the device can be blocked off, for example with a balloon, during the coating process. Over an extended period of time, through its biodegradable characteristics, the film can deliver a controlled amount of a drug that was added to the alginate solution at the point of use, in known concentration over such extended period of time. The drug may be delivered either uniformly or nonuniformly depending on the uniformity of the coating thickness.

For the following examples, non-sterile Monsanto alginate part number HVCR was used whose properties are comparable to the purified form Monsanto part number K8P569 alginate and ProNova part number UP MVG.

In order to produce a biocompatible conformal film solution, application of Good Manufacturing Procedures (GMP) and use of sterile, low endotoxin sodium alginate and sterile, low endotoxin 10% calcium chloride solutions, are recommended to ensure raw material and finished product quality.

In the preferred embodiment of this invention, sodium alginate is mixed with sterile, low-pyrogen water, which is also known as "water for injection," to form a solution. Sodium alginate concentration amounts of about 1% to about 8% by weight and of various molecular weights, in the range of 12,000 to 190,000 with a preferred molecular weight of 120,000 to 190,000 can be used to form a pourable solution tailored to rheological properties desired for the application.

Proper blending techniques are necessary to dissolve the lyophilized sodium alginate in water. A high-shear mixer, which creates vortex, is recommended. The mixing blade is placed off center in the mixing container. The mixing blade is positioned near the bottom of the solution to avoid introducing excessive air. The lyophilized alginate is slowly sifted into the vortex. The application of heat aids in dissolving the alginate powder. While blending, slowly elevate the heat to 135 degrees Fahrenheit and mix for approximately 30 minutes.

The following examples illustrate preferred compositions and formulations that can be used to prepare solutions of alginate, suitable for use in medical implant procedures.

Using the manufacturing procedures outlined above, two solutions of alginate were prepared to determine its physical film properties. The following examples were prepared:

EXAMPLE 1 PART A PART B

PART A	PART B
8% Grade HVCR sodium alginate 92% sterile low-pyrogen water	10% Calcium Chloride Solution

EXAMPLE 2

PART A	PART B
4% Grade HVCR sodium alginate 96% sterile low-pyrogen water	10% Calcium Chloride Solution

The most preferred formula for the embodiment of this inventive device of an in vivo biodegradable conformal film system is the formula used in Example 2 that utilizes 4% sodium alginate (Part A).

Once the alginate polymer solution (in either liquid or gel form) has been prepared by the addition of the polymer to the initial liquid (e.g. water or water and propylene glycol), a drug can be added at the point of use through mixing into the solution. Alternatively, a drug may be added to the liquid to which the polymer is then added to form the solution. A device is then dipped into the solution, coating the device with the drug impregnated solution. Alternatively, the solution may be painted or sprayed onto the device. As previously stated, to restrict the film to the exterior and perforations of a device, the internal diameter of the device can be blocked off, for example with a balloon, during the coating process. The device is then place into sterile, pyrogen-free 10% calcium chloride (Part B) for up to ten minutes, cross-linking the gel and forming a strong, elastic film.

In the above experiments, the elasticity of the film created exceeded 200%. This elasticity makes the film ideal for implantable devices that are expanded once placed at the desired location (i.e., vascular stent).

The invention can be achieved using polymer systems other than alginates such as polymer systems which are in vivo biocompatible and biodegradable and cured with light, such as ultraviolet, or simply dried to form a film. For example, biodegradable PEG polymer (polyethylene glycol) or its derivatives and copolymers that are cured by exposure to ultraviolet light at the point of use may be utilized. Polymers of this nature are commercially available, for example, from Shearwater Polymers of Huntsville, Ala. and are supplied as dry powders that are water soluble and can be mixed with sterile water, or other biocompatible solvents, at the point of use. Bonding of a PEG polymer drug bearing film to a device can be enhanced by the presence of an amino group on the surface which anchors the conformal film.

The invention can also be achieved using previously-mentioned hydrogels such as thermal irreversible hydrogels that are in vivo biocompatible and biodegradable. One example is a PEO/PEG polymer (e.g. Pluronic manufactured by BASF) combined with an alginate, such as sodium alginate, mixed with water to form a solution and cross-linked by interaction with calcium ions (e.g. immersion in 10% by weight calcium chloride). Hydrogel containing films may exhibit less elasticity than the cross-linked sodium alginate films discussed above. However, such hydrogel films are well suited as coatings for devices that are static or unexpanding, such as suture rings

Although the preferred cross-linking agent is calcium chloride, other soluble- substances may be utilized. For example, calcium compounds, such as $CaSO_4$, magnesium compounds such as MgCl or $MgSO_4$, or barium compounds are also contemplated by the present invention for use in cross-linking.

While the invention has been described with reference to preferred embodiments it is to be understood that the invention is not limited to the particulars thereof. The present invention is intended to include modifications which would be apparent to those skilled in the art to which the subject matter pertains without deviating from the spirit and scope of the appended claims.

What is claimed is:

1. A method of producing an implantable drug-deliverable medical device at a point of use, said method comprising:

providing an implantable medical device,

coating said device with an in vivo biocompatible and biodegradable or bioabsorbable or biocrodable liquid or gel solution containing a polymer, said solution comprising a desired dosage amount of one or more predetermined drugs,

converting said liquid or gel solution to a film adhering to said medical device thereby forming said implantable drug-deliverable medical device,

wherein the steps of coating and converting are carried out at said point of use of said implantable medical device.

2. The method of claim 1 wherein said polymer comprises sodium alginate and said solution comprises water and said sodium alginate.

3. The method of claim 2 comprising sodium alginate in an amount of about 1% by weight to about 8% by weight.

4. The method of claim 3 wherein said sodium alginate comprises a molecular weight of about 12,000 to about 190,000.

5. The method of claim 4 wherein said sodium alginate comprises a molecular weight of about 120,000 to about 190,000.

6. The method of claim 3 comprising sodium alginate in an amount of about 4% by weight.

7. The method of claim 3 wherein said sodium alginate comprises mannuronic acid in an amount by weight of 58% to 62% and guluronic acid in an amount by weight of 42% to 38%.

8. The method of claim 2 wherein said one or more drugs are non-water soluble and wherein up to about 10% of said water is replaced with propylene glycol.

9. The method of claim 1 wherein said converting comprises cross-linking said solution to form said film.

10. The method of claim 9 wherein said cross-linking is effected with a calcium chloride solution.

11. The method of claim 10 wherein said calcium chloride solution comprises about 10% by weight calcium chloride.

12. The method of claim 1 wherein said polymer comprises polyethylene oxide, polyethylene glycol and an alginate.

13. The method of claim 1 wherein said polymer comprises polyethylene glycol.

14. The method of claim 1 wherein converting said liquid or gel solution to a film comprises exposing said solution to light.

15. The method of claim 14 wherein said light comprises ultraviolet light.

16. The method of claim 1 wherein said implantable medical device comprises a stent.

17. The device of claim 1 wherein said implantable medical device comprises at least one of pacemaker, vascular graft, suture ring, implantable infusion port, implantable drug delivery pump, orthopedic hardware and appliances, and, neurological stimulating device.

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United States Patent [19]

Loomis

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[54] **BIORESORBABLE COMPOSITIONS FOR IMPLANTABLE PROSTHESES**

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[51] **Int. Cl.**[6] **C08G 63/08**; C08G 63/06; C08G 63/66; C08G 65/02

[52] **U.S. Cl.** **528/354**; 528/361; 424/426; 424/489; 525/54.1; 525/408; 525/413; 525/415; 514/772.1; 514/772.2; 514/773; 514/777

[58] **Field of Search** 528/354, 361; 424/426, 489; 525/54.1, 408, 413, 415; 514/772.1, 772.2, 773, 777

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[57] **ABSTRACT**

Crosslinked compositions formed from a water-insoluble copolymer are disclosed. These compositions are copolymers having a bioresorbable region, a hydrophilic region and at least two crosslinkable functional groups per polymer chain. These compositions are able to form hydrogels in aqueous environments when crosslinked. These hydrogels are good sealants for implantable prostheses when in contact with an aqueous environment. In addition, such hydrogels can be used as delivery vehicles for therapeutic agents.

32 Claims, No Drawings

BIORESORBABLE COMPOSITIONS FOR IMPLANTABLE PROSTHESES

FIELD OF INVENTION

This invention relates generally to coating compositions for medical devices. More particularly, the present invention relates to cross-linked compositions formed from a water insoluble copolymer having a bioresorbable region, a hydrophilic region and at least two crosslinkable functional groups per polymer chain. These compositions when placed in contact with an aqueous environment form hydrogels which are useful as sealants for porous materials and particularly for implantable prostheses. Furthermore, these hydrogels can be used as delivery vehicles for therapeutic agents. Medical devices coated and/or sealed with such hydrogels, processes for forming such devices and methods of making the hydrogels are also disclosed.

BACKGROUND OF THE INVENTION

It is generally known to provide a porous substrate, such as an implantable prosthesis, with a biocompatible, biodegradable sealant or coating composition which initially renders the porous substrate fluid-tight. Over time, such a sealant composition is resorbed and the healing process naturally takes over the sealing function of the sealant composition as tissue ingrowth encapsulates the prosthesis. The art is replete with examples of naturally derived, as well as chemically synthesized sealant compositions.

Natural materials, such as collagen and gelatin, have been widely used on textile grafts. U.S. Pat. Nos. 4,842,575 and 5,034,265 to Hoffman Jr., et al. disclose the use of collagen as a sealant composition for grafts. More recently, co-owned and co-pending U.S. Ser. No. 08/713,801 discloses the use of a hydrogel or sol-gel mixture of polysaccharides for rendering fluid-tight porous implantable devices. Such sealant compositions are beneficial in that they are able to seal an implantable device without the need for chemical modification of the surface thereof and provide improved bioresorbability as the healing process occurs. Furthermore, fibrin, an insoluble protein formed during the blood clotting process, has also been used as a sealant for porous implantable devices.

The use of such biologically derived sealant compositions, however, suffers from several drawbacks. One such drawback is the difficulty in producing consistent coatings due to variations inherent in natural materials. Another drawback is that the body may identify such compositions as foreign and mount an immune response thereto. Thus, biologically-based sealant compositions can cause inflammation, as well as infection at or around the site of implantation, which can lead to life-threatening complications.

Accordingly, attempts have been made to design sealant systems from chemically synthesized materials which are easier to manufacture and control the desired characteristics and qualities and which have less potential for causing adverse biological reactions. For example, U.S. Pat. No. 4,826,945 to Cohn et al. discloses synthetically produced resorbable block copolymers of poly(α-hydroxy-carboxylic acid)/poly(oxyalkylene) which are used to make absorbable sutures, wound and burn dressings and partially or totally biodegradable vascular grafts. These copolymers, however, are not crosslinked. The poly(alkylene) segments of such bio-absorbable copolymers are disclosed to be water-soluble so that the body can excrete the degraded block copolymer compositions. See also, Younes, H. and Cohn, D., *J Biomed. Mater. Res.* 21, 1301–1316 (1987) and Cohn, D. and Younes, H., *J Biomed. Mater. Res.* 22, 993–1009 (1988). As set forth above, these compositions are uncrosslinked and, as a consequence, are relatively quickly bio-absorbed. Moreover, these uncrosslinked compositions generally require the presence of crystalline segments to retain their hydrogel-like consistency. As a result of such crystalline segments, these compositions have limited utility as sealants for vascular grafts.

Furthermore, U.S. Pat. No. 4,438,253 to Casey et al. discloses tri-block copolymers produced from the transesterification of poly(glycolic acid) and an hydroxyl-ended poly(alkylene glycol). Such compositions are disclosed for use as resorbable monofilament sutures. The flexibility of such compositions is controlled by the incorporation of an aromatic orthocarbonate, such as, tetra-p-tolyl orthocarbonate into the copolymer structure. The strength and flexibility which makes such a composition useful as a suture, however, does not necessarily make it appropriate for use as a sealant for a porous implantable prosthesis. Moreover, these tri-block copolymers are substantially uncross-linked. Thus, while compositions are somewhat hydrophilic, they do not form hydrogels.

Accordingly, attempts have been made to engineer biocompatible hydrogel compositions whose integrity can be controlled through crosslinking. For example, U.S. Pat. Nos. 5,410,016 and 5,529,914 to Hubbell et al. disclose water-soluble systems which when crosslinked utilize block copolymers having a water-soluble central block segment sandwiched between two hydrolytically labile extensions. Such copolymers are further end-capped with photopolymerizable acrylate functionalities. When crosslinked, these systems become hydrogels. The water soluble central block of such copolymers can include poly(ethylene glycol); whereas, the hydrolytically labile extensions can be a poly (α-hydroxy acid), such as, polyglycolic acid or polylactic acid. See, Sawhney, A. S., Pathak, C. P., Hubbell, J. A., *Macromolecules* 1993, 26, 581–587.

Furthermore, U.S. Pat. No. 5,202,413 to Spinu discloses biodegradable multi-block copolymers having sequentially ordered blocks of polylactide and/or polyglycolide produced by ring-opening polymerization of lactide and/or glycolide onto either an oligomeric diol or a diamine residue followed by chain extension with a di-functional compound, such as, a diisocyanate, diacylchloride or dichlorosilane. The general structure of such a composition is R—(A-B-A-L)$_x$-A-B-A-R, where A is a polyhydroxy acid, such as polylactide, polyglycolide or a copolymer thereof, B is an oligomeric diol or diamine residue, L is a diacyl residue derived from an aromatic diacyl halide or diisocyanate and R is H or an end-capping group, such as an acyl radical. A major difference between the compositions set forth in the Spinu '413 patent and those described by the Cohn references supra is that Spinu uses lactide blocks whereas Cohn uses lactic acid blocks. Furthermore, like the Cohn copolymers, the copolymers described in the Spinu '413 patent are not crosslinkable.

In general, all of the synthetic compositions set forth above describe copolymers having one or more segments which are water-soluble. Accordingly, many of the compositions described by these references are intended to be rapidly biodegraded by the body.

Thus, there is a need for water-insoluble, fully crosslinkable polymeric materials which are easily synthesized and

provide controlled bioresorption in vivo. Moreover, there is a need for improved, cost-efficient synthetic sealant compositions for porous implantable prostheses which are characterized by their ability to self-emulsify and form stable low viscosity emulsions. There is a further need for sealant compositions which are quickly cured, exist as hydrogels in an aqueous environment and which remain flexible while dehydrated without the need for an external plasticizer. The present invention is directed to meeting these and other needs.

SUMMARY OF THE INVENTION

In one embodiment of the present invention, there is provided a covalently crosslinkable composition. This composition includes a water-insoluble copolymer which has a bioresorbable region, a hydrophilic region and a plurality of crosslinkable functional groups per polymer chain.

In another embodiment of the present invention, there is provided a medical device which has on at least one surface thereof a bioresorbable coating composition. This composition includes a hydrogel formed from the crosslinking of a polymer containing a bioresorbable region, a hydrophilic region, a plurality of crosslinkable functional groups and a crosslinking agent.

In a further embodiment of the present invention, there is provided a process for forming a hydrogel. This process includes providing an aqueous emulsion of a water-insoluble copolymer. This water-insoluble copolymer includes a bioresorbable region, a hydrophilic region, a plurality of crosslinkable functional groups per polymer chain and a crosslinking agent. Activation of the crosslinking agent crosslinks the copolymer composition and forms the hydrogel.

In yet a further embodiment of the present invention, there is provided a process for forming a medical device coated with a hydrogel. The hydrogel is formed from an aqueous emulsion which includes a water-insoluble copolymer having a bioresorbable region, a hydrophilic region, a plurality of crosslinkable functional groups per polymer chain and a crosslinking agent. This process includes applying the hydrogel to the medical device and then activating the crosslinking agent in a humid environment.

DETAILED DESCRIPTION OF THE INVENTION

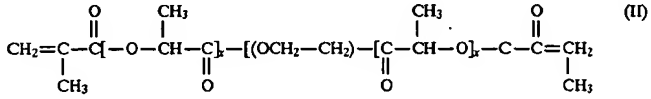
The present invention is directed to covalently crosslinkable compositions formed from water-insoluble copolymers. The copolymers of the present invention include a bioresorbable region, a hydrophilic region and a plurality of crosslinkable functional groups per polymer chain. When uncrosslinked, the copolymer compositions form stable aqueous emulsions. Once crosslinked, however, such compositions form hydrogels in the presence of water. Hydrogels formed from the compositions of the present invention can serve as coatings for a medical device and/or as a therapeutic agent delivery vehicle.

The copolymers of the present invention are multi-block copolymers including, for example, di-block copolymers, tri-block copolymers, star copolymers, and the like. For purposes of illustration only, a typical tri-block copolymer of the present invention may have the following general formula:

$$xABAx \qquad (I)$$

wherein A is the bioresorbable region, B is the hydrophilic region and x is the crosslinkable functional group.

A more specific example of a copolymer useful in the present inventive compositions has the following chemical structure:



(II)

wherein x is from about 10 to about 50 and y is from about 50 to about 300, so long as the composition remains water-insoluble as a whole.

One required feature of the present invention is that the crosslinkable copolymer composition be water-insoluble. For purposes of the present invention, "water-insoluble" is intended to mean that the copolymers of the present invention are substantially insoluble in water or water-containing environments. Thus, although certain regions or segments of the copolymer may be hydrophilic or even water-soluble, however, the copolymer molecule, as a whole, does not by any substantial measure dissolve in water or water-containing environments.

As set forth above, the water-insoluble copolymer includes a bioresorbable region. For purposes of the present invention, the term "bioresorbable" means that this region is capable of being metabolized or broken down and resorbed and/or eliminated through normal excretory routes by the body. Such metabolites or break-down products should be substantially non-toxic to the body.

The bioresorbable region is preferably hydrophobic. In another preferred embodiment, however, the bioresorbable region may be designed to be hydrophilic so long as the copolymer composition as a whole is not rendered water-soluble. Thus, the bioresorbable region is designed based on the requirement that the copolymer, as a whole, must remain water-insoluble. Accordingly, the relative properties, i.e., the kinds of functional groups contained by, and the relative proportions of the bioresorbable region, and the hydrophilic region are selected to ensure that the present compositions remain water-insoluble.

The copolymers of the present invention form a stable aqueous emulsion. For purposes of the present invention, the terms "emulsion", "emulsifiable" and "self-emulsifying" refer to the ability of the copolymers of the present composition to form an emulsion, i.e., a colloidal suspension of one liquid in another, without the requirement of an emulsifying agent to stabilize the emulsion. Although emulsifying agents are not required by the present invention, their use is not excluded in appropriate circumstances if so desired by the skilled artisan. The relative proportions or ratios of the bioresorbable and hydrophilic regions, respectively are specifically selected to render the block copolymer composition water-insoluble. Furthermore these compositions are sufficiently hydrophilic to form a hydrogel in aqueous environments when crosslinked. Such hydrogels, as set forth in more detail below, can form a fluid-tight barrier when applied to a medical device. The specific ratio of the two regions of the block copolymer composition of the present invention will of course vary depending upon the intended application and will be affected by the desired physical

properties of the porous implantable prosthesis, the site of implantation, as well as other factors. For example, the composition of the present invention remains substantially water-insoluble when the ratio of the water-insoluble region to the hydrophilic region is from about 10:1 to about 1:1, on a percent by weight basis.

The bioresorbable region of the present invention can be designed to be hydrolytically and/or enzymatically cleavable. For purposes of the present invention, "hydrolytically cleavable" refers to the susceptibility of the copolymer, especially the bioresorbable region, to hydrolysis in water or a water-containing environment. Similarly, "enzymatically cleavable" as used herein refers to the susceptibility of the copolymer, especially the bioresorbable region, to cleavage by endogenous or exogenous enzymes.

Based on the characteristics set forth above, a number of different compositions can be utilized as the bioresorbable region. Thus, the bioresorbable region includes without limitation, for example, poly(esters), poly(hydroxy acids), poly(lactones), poly(amides), poly(ester-amides), poly (amino acids), poly(anhydrides), poly(ortho-esters), poly (carbonates), poly(phosphazines), poly(thioesters), polysaccharides and mixtures thereof. Furthermore, the bioresorbable region can also be, for example, a poly (hydroxy) acid including poly (α-hydroxy) acids and poly (β-hydroxy) acids. Such poly(hydroxy) acids include, for example, polylactic acid, polyglycolic acid, polycaproic acid, polybutyric acid, polyvaleric acid and copolymers and mixtures thereof.

As set forth above, the present composition also includes a hydrophilic region. For purposes of the present invention, "hydrophilic" is used in the classical sense of a material or substance having an affinity for water. Although the present composition contains an hydrophilic region, this region is designed and/or selected so that the composition as a whole, remains water-insoluble at all times.

When placed within the body, the hydrophilic region can be processed into excretable and/or metabolizable fragments. Thus, the hydrophilic region can include without limitation, for example polyethers, polyalkylene oxides, polyols, poly(vinyl pyrrolidine), poly(vinyl alcohol), poly (alkyl oxazolines), polysaccharides, carbohydrates, peptides, proteins and copolymers and mixtures thereof. Furthermore, the hydrophilic region can also be, for example, a poly(alkylene) oxide. Such poly(alkylene) oxides can include, for example, poly(ethylene) oxide, poly (propylene) oxide and mixtures and copolymers thereof.

As set forth above, the composition of the present invention also includes a plurality of crosslinkable functional groups. Any crosslinkable functional group can be incorporated into the present compositions so long as it permits or facilitates the formation of a hydrogel. Preferably, the crosslinkable functional groups of the present invention are olefinically unsaturated groups. Suitable olefinically unsaturated functional groups include without limitation, for example, acrylates, methacrylates, butenates, maleates, allyl ethers, allyl thioesters and N-allyl carbamates. Preferably, the crosslinking agent is a free radical initiator, such as for example, 2,2'-Azobis (N,N'dimethyleneisobutyramidine) dihydrochloride.

The crosslinkable functional groups can be present at any point along the polymer chain of the present composition so long as their location does not interfere with the intended function thereof. Furthermore, the crosslinkable functional groups can be present in the polymer chain of the present invention in numbers greater than two, so long as the intended function of the present composition is not compromised.

Preferably, however, at least two olefinically unsaturated functional groups are present on the polymer chain of the present composition. As set forth above, the number of olefinically unsaturated functional groups present on the polymer chain can be increased beyond two, depending upon the particular application. Although the olefinically unsaturated functional groups can be positioned anywhere within the polymer chain of the present composition, it is preferred that at least one olefinically unsaturated functional group be positioned at a terminus of the polymer chain. More preferably, an olefinically unsaturated group is positioned at both terminal ends of the polymer chain. Furthermore, as there are at least two functional groups present in the present composition, the functional groups contained therein can be the same or different.

Crosslinking of compositions of the present invention is accomplished through the crosslinkable functional groups. These functional groups are activated to crosslink the copolymer composition by a variety of crosslinking initiators. These crosslinking initiators can include, for example, high energy radiation, thermal radiation and/or visible light. The composition of the present invention can also include free radical initiators. Such free radical initiators can include, for example, a peroxide or an azo compound.

In the present invention, the composition is crosslinked in an aqueous medium. Furthermore, when crosslinked, the copolymer composition is able to form a hydrogel. The hydrogels of the present invention are polymeric materials that swell in water without dissolving and that retain a significant amount of water in their structures. Such compositions have properties intermediate between liquid and solid states. Hydrogels also deform elastically and recover, yet will often flow at higher stresses. Thus, for purposes of this invention hydrogels are water-swollen, three-dimensional networks of hydrophilic polymers. These hydrogel compositions are not as transient as, and are more controllable than the prior art non-crosslinked sealant compositions described above. Thus, the present compositions have distinct advantages over the prior art and are able to function as superior sealants, for example, porous implantable prostheses, as well as, delivery devices for certain therapeutic agents.

In one embodiment of the invention, a therapeutic agent, such as for example a drug or bio-active agent, may be incorporated into the composition of the present invention for controlled release as the composition is bioresorbed. Thus, the present composition can be used to target therapeutic agents to specific sites in the body. Furthermore, the present composition can be engineered to bioresorb at a certain rate by controlling the ratio of the bioresorbable to the hydrophilic regions, as well as by controlling the degree of crosslinking thereof. Thus, the present compositions are able to delivery controlled quantities of a therapeutic agent to a specific site in the body as the block copolymer is bioresorbed.

Any drug or bio-active agent may be incorporated into the composition of the present invention provided that it does not interfere with the required characteristics and functions of the composition. Examples of suitable drugs or bio-active agents may include, for example, without limitation, thrombo-resistant agents, antibiotic agents, anti-tumor agents, anti-viral agents, anti-angiogenic agents, angiogenic agents, anti-inflammatory agents, cell cycle regulating agents, their homologs, derivatives, fragments, pharmaceutical salts and combinations thereof.

Useful thrombo-resistant agents can include, for example, heparin, heparin sulfate, hiradin, hyaluronic acid, chon-

droitin sulfate, dermnatan sulfate, keratin sulfate, lytic agents, including urokinase and streptokinase their homologs, analogs, fragments, derivatives and pharmaceutical salts thereof.

Useful antibiotics can include, for example, penicillins, cephalosporins, vancomycins, aminoglycosides, quinolones, polymyxins, erythromycins, tetracyclines, chloramphenicols, clindamycins, lincomycins, sulfonamides their homologs, analogs, fragments, derivatives, pharmaceutical salts and mixtures thereof.

Useful anti-tumor agents can include, for example, paclitaxel, docetaxel, alkylating agents including mechlorethamine, chlorambucil, cyclophosphamide, melphalan and ifosfamide; antimetabolites including methotrexate, 6-mercaptopurine, 5-fluorouracil and cytarabne; plant alkaloids including vinblastine, vincristine and etoposide; antibiotics including doxorubicin, daunomycin, bleomycin, and mitomycin; nitrosureas including carmustine and lomustine; inorganic ions including cisplatin; biological response modifiers including interferon; enzymes including asparaginase; and hormones including tamoxifen and flutamide their homologs, analogs, fragments, derivatives, pharmaceutical salts and mixtures thereof.

Useful anti-viral agents can include, for example, amantadines, rimantadines, ribavirins, idoxuridines, vidarabines, trifluridines, acyclovirs, ganciclovirs, zidovudines, foscarnets, interferons their homologs, analogs, fragments, derivatives, pharmaceutical salts and mixtures thereof.

In another embodiment of the present invention, there is provided a medical device having on at least one surface thereof a bioresorbable coating composition. This coating composition includes a hydrogel which is formed from the crosslinking of a polymer containing a bioresorbable region, a hydrophilic region, a plurality of crosslinked functional groups and a crosslinking agent, as set forth previously.

The bioresorbable coating composition of the present invention can be applied as coatings to medical devices. In particular, the present bioresorbable coating compositions are intended to coat medical devices made from implantable materials. These bioresorbable coatings are capable of rendering fluid-tight porous medical devices such as conduits, vascular grafts, textile materials, polymeric films and the like. For purposes of the present invention, the term "fluid-tight" refers to the specific porosity of a material, such as a porous vascular or endovascular graft. Porosity of textile materials is often measured with a Wesolowski Porosity tester. With this apparatus, a graft is tied off at one end and the free end is attached to a valve on a porometer so that the graft hangs freely in a vertical position. Then, water is run through the graft for one minute and the water that escapes from the graft is collected and measured. The specific porosity of the graft is then calculated according to the following formula:

$$P = \frac{V}{A}$$

where V is the volume of water collected in ml/min and A is the surface area of the graft exposed to water in cm^2. A specific porosity of ≤ 1.0 ml/min/cm^2 is considered an acceptable amount of leakage for an implantable vascular graft. Accordingly, for purposes of this invention, a substantially fluid-tight graft means a graft with a specific porosity, after impregnation with a sealant of the present invention, of ≤ 1.0 ml/min/cm^2. Porosities meeting and exceeding the acceptable specific porosity criteria set forth above are achieved through the use of certain block copolymers described herein having polyether-polyester segments.

Implantable materials useful in the present invention can include, for example polymeric compositions, non-polymeric compositions and combinations thereof. The polymeric material can include, for example, olefin polymers including polyethylene, polypropylene, polyvinyl chloride, polytetrafluoroethylene, fluorinated ethylene propylene copolymer, polyvinyl acetate, polystyrene, poly (ethylene terephthalate), polyurethane, polyurea, silicone rubbers, polyamides, polycarbonates, polyaldehydes, natural rubbers, polyester copolymers, styrene-butadiene copolymers and combinations thereof. Non-polymeric implantable materials can include, for example, ceramics, metals, inorganic glasses, pyrolytic carbon and combinations thereof. The compositions set forth hereinabove for the implantable substrate material of the present invention are intended to be exemplary only and should not be construed to limit in any way the types of materials to which the present bioresorbable coatings can be applied.

As set forth above, these implantable materials are used to manufacture medical devices, such as for example, endoprostheses. Grafts, stents and combination graft-stent devices are contemplated. Preferably these medical devices are vascular or endovascular grafts. Useful vascular or endovascular grafts include those which are knitted, braided or woven textiles, and may have velour or double velour surfaces. Alteratively, the medical device can be manufactured from an extruded polymer, such as polytetrafluoroethylene (PTFE), polyethylene terephthalate (PET), fluorinated ethylene propylene copolymer (FEP), polyurethane, silicone and the like. Composite structures are also contemplated.

In another preferred embodiment, the medical device may be a catheter, a guidewire, a trocar, an introducer sheath or the like. When coated onto such devices, the composition of the present invention imparts increased bio-compatibility to one or more surfaces thereof. Furthermore, when the present composition includes a drug or bio-active agent, specific therapeutic effects can be imparted to the surfaces of such devices. Moreover, the hydrophilic region of the present composition can impart increased lubriciousness to the surfaces of, e.g., a guidewire or other similar device.

Thus, any medical device to which the bioresorbable coating composition can adhere can be used in conjunction with the present invention. Accordingly, the examples of implantable materials and medical devices set forth hereinabove are for purposes of illustration only and are not intended to limit the scope of the materials and devices to which the present bioresorbable coatings can be applied or otherwise associated therewith.

In another embodiment of the present invention, there is provided a process for forming a hydrogel. This process includes: (i) providing an aqueous emulsion of a water-insoluble copolymer which contains a bioresorbable region, a hydrophilic region, a plurality of crosslinkable functional groups per polymer chain and a crosslinking agent; and (ii) activating the crosslinking agent, as set forth previously. In this process, the crosslinkable functional groups can be, but are not limited to, olefinically unsaturated groups. As set forth previously, the crosslinking agent can be a free radical initiator, an azo or a peroxide composition. Still further, the crosslinking agent can be, for example, thermally or photochemically activated.

In yet another embodiment of the present invention, there is provided a process for forming a medical device coated with a hydrogel. As set forth previously, this hydrogel is formed from an aqueous emulsion which includes a water-insoluble copolymer. This copolymer includes a bioresorbable region, a hydrophilic region, a plurality of crosslinkable

functional groups per polymer chain and a crosslinking agent. Accordingly, this process includes applying the hydrogel to the medical device and then activating the crosslinking agent in a humid environment.

Although, the crosslinking agent can be activated in both humid and non-humid environments, it is preferred that the activation take place in humid environments. Preferably, the humid environment contains from about 20% to about 100% water. More preferably, the humid environment contains from about 60% to about 100% water.

The hydrogels formed by this process can be packaged and stored in a variety of ways. For example, the hydrogel can be maintained in a hydrated state for an extended period of time. Alternatively, the hydrogel can be dehydrated and stored in an essentially desiccated state until use.

As set forth previously, a therapeutic agent, such as for example, a drug or bio-active agent can be added to the emulsion for targeted, timed release of such agents in the body. Examples of types of therapeutic agents which can be incorporated into the emulsion have been set forth above.

The following examples are set forth to illustrate the copolymer compositions of the present invention. These examples are provided for purposes of illustration only and are not intended to be limiting in any sense.

EXAMPLE 1

A polymer (Polymer A) according to the present invention was synthesized as follows:

125.0 gm poly(ethylene glycol-co-propylene glycol) (75 wt % ethylene glycol, M_n=12,000) was charged to a 4-necked reaction flask equipped with a Dean-Stark water trap, a water-cooled condenser, a thermometer, and a gas inlet/a gas outlet system which allowed for the controlled flow of nitrogen. While maintaining a nitrogen atmosphere, 660 ml anhydrous toluene was added to the flask and the mixture was heated and reflux was maintained for 3–4 hours. During this period any water present was collected in the Dean-Stark trap (approximately 10% of the original toluene was also removed during this azeotropic water removal). The flask was allowed to cool to room temperature and 30.4 gm d,l-lactide was added to the flask followed by 50 mg of stannous 2-ethylhexanoate catalyst (1% solution in anhydrous toluene). The reaction mixture was heated to reflux for 6 hours and was allowed to cool to room temperature.

5.28 gm of triethylamine was added to the mixture. After 5 minutes of stirring, 4.72 gm of acryloyl chloride was slowly added to the flask. The mixture was then heated to reflux for 7 hours followed by cooling to room temperature. Unreacted acryloyl chloride was quenched with 15 ml of methanol. Approximately 110 mg of 4-methoxy phenol was added to the flask as a free-radical stabilizer.

The solution was filtered to remove triethylamine hydrochloride and the amount of solvent was reduced in vacuo to approximately half of the original volume. This solution was then precipitated into ether, filtered and the remaining solvent was removed in vacuo to afford the polymer as a viscous oil which is substantially water-insoluble.

EXAMPLE 2

Another polymer (Polymer B) according to the present invention was synthesized as set forth in Example 1 with the following exceptions. 60.07 gm of l-lactide was substituted for the d,l-lactide of Example 1 and the amount of stannous 2-ethylhexanoate was decreased to 40 mg. The resulting Polymer B was a waxy solid which was substantially water-insoluble.

EXAMPLE 3

Polymer C according to the present invention was synthesized as set forth in Example 1 with the following exceptions. The amount of d,l-lactide was increased to 71.2 gm, the amount of stannous 2-ethylhexanoate was decreased to 40 gm, the amount of acryl chloride was increased to 22.63 gm and the amount of triethylamine was increased to 25.63 gm. The resulting Polymer C was an oil which was substantially water-insoluble.

EXAMPLE 4

Polymer D according to the present invention was synthesized as set forth in Example 1 with the following exceptions. The amount of d,l-lactide was increased to 22.5 gm and the amount of stannous 2-ethylhexanoate was also decreased to 40 mg. The resulting Polymer D was a viscous oil that was substantially water-insoluble.

EXAMPLE 5

An aqueous emulsion (20% solids) was prepared by dispersing Polymer D and Vazo™ 044 (13.4 mg Vazo/1.0 gm. polymer) in water with rapid stirring. The mixture was transferred to a shallow Teflon™ mold (9 cm×9 cm×1 cm), which was sealed with a glass cover plate and placed in an oven at 60° C. for approximately 60 minutes.

The resulting hydrogel was demolded and dehydrated in vacuo to afford a thick elastic film with a hardness of Shore A=28. Stress-strain (Instron testing with crosshead speed= 200 mm/min.), tensile strength at break (T_b)=50 psi (0.35 Mpa) and % elongation at break (%E_B)=585. The water uptake of this dehydrated hydrogel was determined as follows:

time (hr.)	weight gm.	% weight gain
0	0.2275	
1	1.9145	590
2	2.5295	812
24	3.5325	1174

EXAMPLE 6

A fabric suitable for use in medical procedures was coated with Polymer D of the present invention. In particular, a 1 inch×3 inch rectangle of a knitted polyester medical fabric was impregnated by immersing it for 5.0 minutes in a degassed aqueous emulsion containing 1.0 gm of Polymer D and 13.4 mg. Vazo™ 044 dispersed in 4.0 ml. de-ionized water. The impregnated fabric was then passed twice through a soft rubber wringer to remove excess emulsion. The impregnated fabric was then placed in an environmental chamber maintained at about 60°–65° C. and 100% relative humidity under nitrogen for 60 minutes. The sample was then cooled to room temperature, washed twice (each wash was 15 minutes) with distilled water, then dried to constant weight.

EXAMPLE 7

The water porosity of the coated medical fabric of Example 6 was determined in a laboratory apparatus as described in AAMI Standards & Recommended Procedures, 1989, Reference Book; and in "Evaluation of Tissue and Prosthetic Vascular Grafts", p. 62, Charles Thomas, Publisher, Springfield, Ill., 1962. In the water porosity test, the coated medical fabric of Example 6 was placed over a

hole, and a metal plate, containing a concentric hole of the same size, was clamped over the sample. Water was permitted to flow through the fabric, and the pressure was adjusted until the specific test pressure was reached. Porosity was calculated as follows:

$$\text{Porosity}=Q/A$$

where,

Q=flow rate through the sample in cc/minute@120 mm Hg, and

A=the cross-sectional area in cm^2 of the hole.

The following table sets forth the porosity data for the medical fabric coated with Polymer D.

Water Porosity of Hydrogel Coated Knitted Polyester Fabric

Sample	Number of Coats	Sealant as wt % of Total Specimen	Porosity (ml/min./cm^2)
uncoated control			559.0
specimen 1 (20% solids)	1	20.7	0.0
specimen 2 (20% solids)	1	21.0	2.6
specimen 3 (20% solids)	2	29.9	0.0
specimen 4 (20% solids)	3	19.1	9.4

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

What is claimed is:

1. A covalently crosslinkable composition comprising a water-insoluble copolymer having (i) a bioresorbable region; (ii) a hydrophilic region; and (iii) a plurality of crosslinkable functional groups per polymer chain.

2. The composition of claim 1, wherein said copolymer forms a stable aqueous emulsion.

3. The composition of claim 1, wherein the ratio of said bioresorbable region to said hydrophilic region is from about 10:1 to about 1:1 on a percent by weight basis.

4. The composition of claim 1, wherein the relative properties and proportions of said bioresorbable region and said hydrophilic region are selected to render said composition insoluble in water.

5. The composition of claim 1, wherein said bioresorbable region is hydrophobic.

6. The composition of claim 1, wherein said bioresorbable region has hydrophilic character without rendering the polymer water-soluble.

7. The composition of claim 1, wherein said bioresorbable region is hydrolytically and/or enzymatically cleavable.

8. The composition of claim 1, wherein said bioresorbable region is selected from the group consisting of poly(esters), poly(hydroxy acids), poly(lactones), poly(amides), poly (ester-amides), poly (amino acids), poly(anhydrides), poly (orthoesters), poly(carbonates), poly(phosphazines), poly (phosphoesters), poly(thioesters), polysaccharides and mixtures thereof.

9. The composition of claim 1, wherein said bioresorbable region is a poly(hydroxy) acid.

10. The composition of claim 9, wherein said poly (hydroxy) acid is formed from material selected from the group consisting of polylactic acid, polyglycolic acid, polycaproic acid, polybutyric acid, polyvaleric acid and copolymers and mixtures thereof.

11. The composition of claim 1, wherein said hydrophilic region is selected from the group consisting of polyethers, polyalkylene oxides, polyols, poly(vinylpyrrolidine), poly (vinyl alcohol), poly(alkyl oxazolines), polysaccharides, carbohydrates, peptides, proteins and copolymers and mixtures thereof.

12. The composition of claim 1, wherein said hydrophilic region forms an excretable and/or metabolizable fragment.

13. The composition of claim 1, wherein said hydrophilic region is a poly(alkylene) oxide.

14. The composition of claim 13, wherein said poly (alkylene) oxide is selected from the group consisting of poly(ethylene) oxide, poly(propylene) oxide and mixtures and copolymers thereof.

15. The composition of claim 1, wherein said plurality of crosslinkable functional groups are olefinically unsaturated groups.

16. The composition of claim 15, wherein at least one of said olefinically unsaturated functional groups is positioned at a terminus of said polymer chain.

17. The composition of claim 15, wherein said olefinically unsaturated functional groups are selected from the group consisting of acrylates, methacrylates, butenoates, maleates, allyl ethers, allyl thioesters and N-allyl carbamates.

18. The composition of claim 1 being crosslinked by high energy or thermal radiation.

19. The composition of claim 1 being crosslinked by visible light.

20. The composition of claim 1 further including a free radical initiator.

21. The composition of claim 20, wherein said free radical initiator is a peroxide.

22. The composition of claim 20, wherein said free radical initiator is an azo compound.

23. The composition of claim 1, wherein said copolymer is crosslinked in an aqueous medium.

24. The composition of claim 23, wherein a crosslinked polymer forms a hydrogel.

25. The composition of claim 23, wherein said hydrophilic region is water-swellable.

26. The composition of claim 24, wherein said hydrogel is useful as a coating for a medical device.

27. The composition of claim 24, wherein said hydrogel is useful as a drug or bio-active agent delivery vehicle.

28. The composition of claim 27, wherein said drug or bio-active agent is selected from the group consisting of thrombo-resistant agents, antibiotic agents, anti-tumor agents, antiviral agents, anti-angiogenic agents, angiogenic agents, anti-inflammatory agents, cell cycle regulating agents and chemically modified equivalents and combinations thereof.

29. The composition of claim 28, wherein said drug or bio-active agent is selected from the group of thrombo-resistant agents consisting of heparin, heparin sulfate, hirudin, hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate, lytic agents, urokinase, streptokinase, and chemically modified equivalents and combinations thereof.

30. The composition of claim 28, wherein said drug or bio-active agent is selected from the group of antibiotic agents consisting of penicillins, cephalosporins, vancomycins, aminoglycosides, quinolones, polymyxins, erthromycins, tetracyclines, chloramphenicols, clindamycins, lincomycins, sulfonamides, and chemically modified equivalents and combinations thereof.

31. The compositions of claim 28, wherein said drug or bio-active agent is selected from the group of antibiotic agents consisting of paclitaxel, mechlorethamine, chlorambucil, cyclophosphamide, melphalan, ifosfamide, methotrexate, 6-mercaptopurine, 5-fluorouracil, cytarabine, vinblastine, vincristine, etoposide, doxorubicin, daunomycin, bleomycin, mitomycin, carmustine, lomustine, cisplatin, interferon, asparaginase, tamoxifen, flutamide and chemically modified equivalents and combinations thereof.

32. The compositions of claim 28, wherein said drug or bio-active agent is selected from the group of anti-viral agents consisting of amantadines, rimantadines, ribavirins, idoxuridines, vidarabines, trifluridines, acyclovirs, ganciclovirs, zidovudines, foscarnets, interferons, and chemically modified equivalents and combinations thereof.

* * * * *

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United States Patent [19]

Dayton

[11] Patent Number: 5,449,382

[45] Date of Patent: Sep. 12, 1995

[54] MINIMALLY INVASIVE BIOACTIVATED ENDOPROSTHESIS FOR VESSEL REPAIR

[76] Inventor: Michael P. Dayton, 14802 Hadleigh Way, Tampa, Fla. 33624

[21] Appl. No.: 204,947

[22] Filed: Mar. 2, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 971,217, Nov. 4, 1992, abandoned.

[51] Int. Cl.[6] A61F 2/06

[52] U.S. Cl. 623/1; 623/11; 623/12; 606/194

[58] Field of Search 606/191, 192, 194, 198; 623/1, 11, 12

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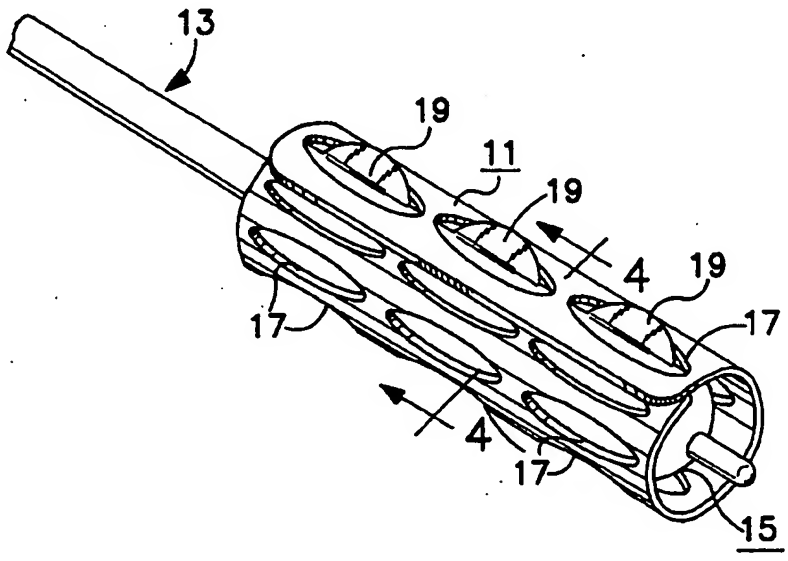
Primary Examiner—Stephen C. Pellegrino
Assistant Examiner—Michael Peffley
Attorney, Agent, or Firm—John S. Munday; Stephen G. Stanton

[57] ABSTRACT

A minimally invasive bioactivated endoprosthesis device for vessel repair. The device comprises a stent which is formed from metal or polymers into a predetermined shape which includes a plurality of holes patterned with a desired size, shape and number to provide a desired bending modulus. The stent is then coated with a polymer or is formed from a polymer which contains a bioactive substance which achieves an equilibrium with the surrounding body tissues or fluids, with the equilibrium being controlled by charge distribution, concentration and molecular weight of the bioactive substance in relation to the pore size of the polymeric carrier for controlled prolonged release of said bioactive substance. The bioactive substance may be selected from the group of heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments. The stent itself may take several distinct configurations, all of which have a predetermined biasing force acting on the diameter of the stent. Preferred is a rolled stent which is provided with a coiled shape to which it tends to return when expanded. Locking tabs are provided to engage the some of the plurality of holes at the maximum expanded size to prevent return to the smaller diameter coiled shape. Alternatively the predetermined bias of the stent may be the expanded size so that the stent is coiled against this bias during insertion.

13 Claims, 3 Drawing Sheets



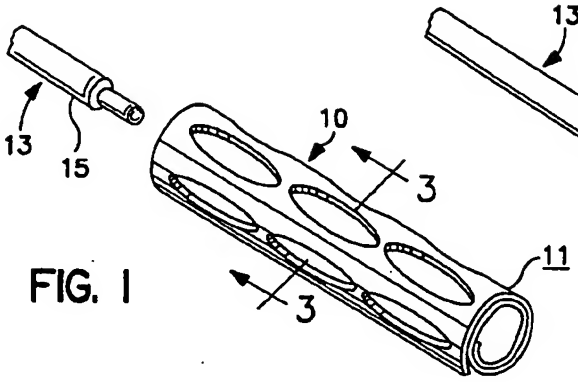


FIG. 1

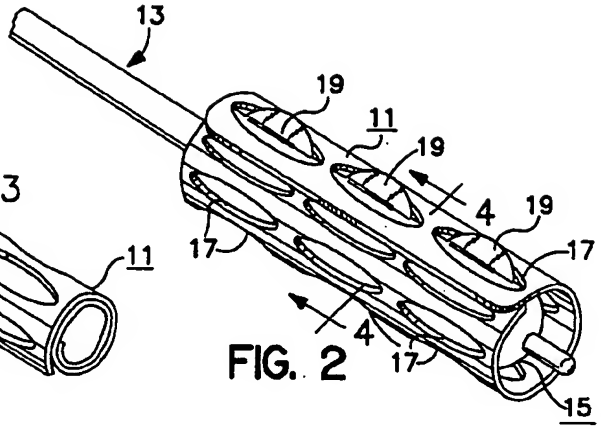


FIG. 2

FIG. 3

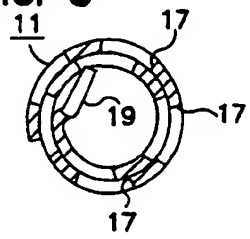


FIG. 4

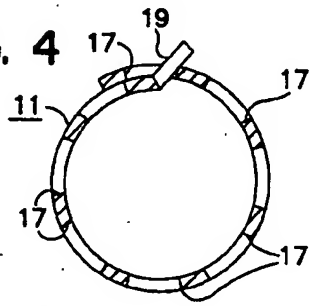


FIG. 6

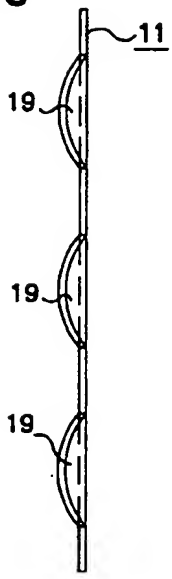


FIG. 5

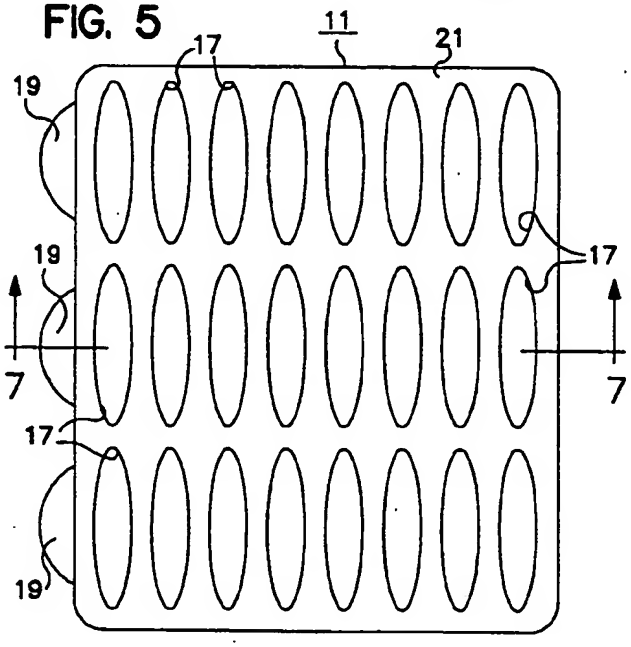


FIG. 7

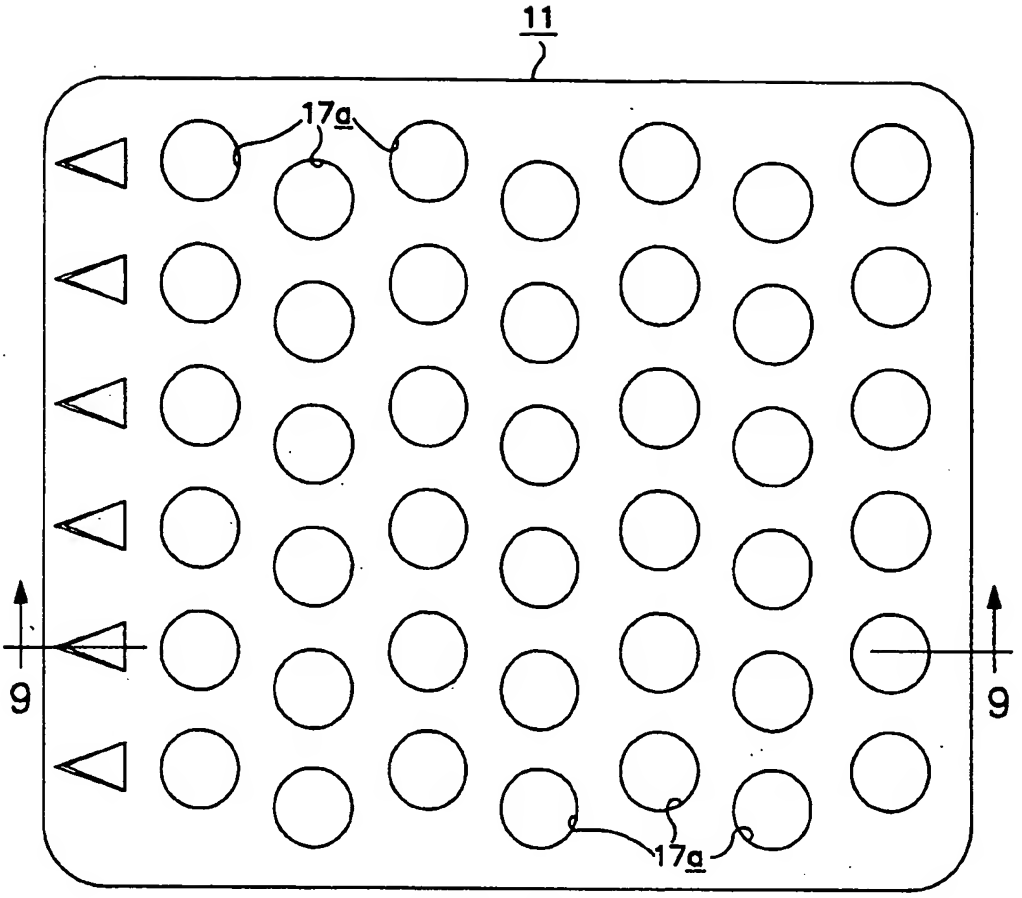


FIG. 8

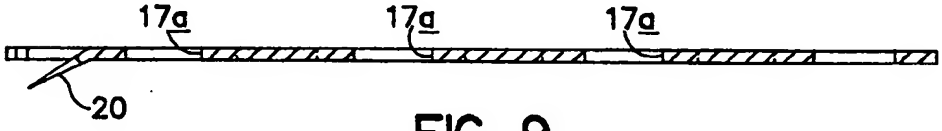


FIG. 9

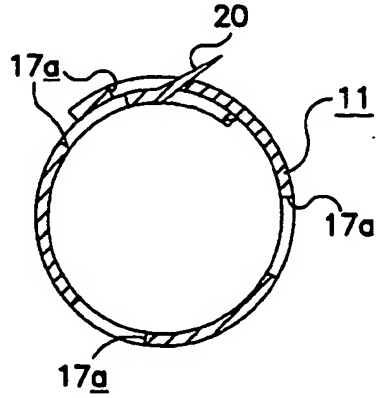


FIG. 10

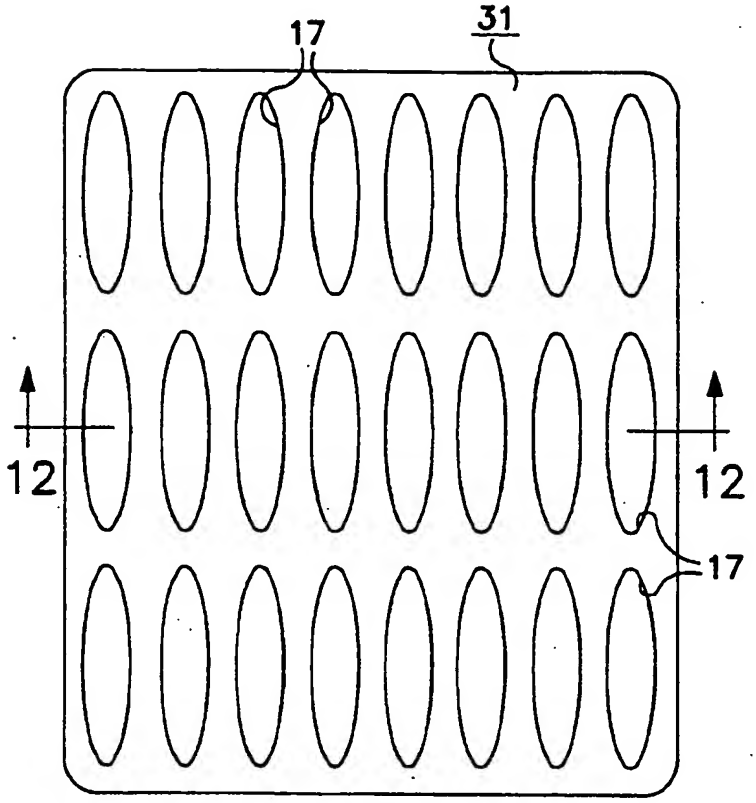


FIG. 11

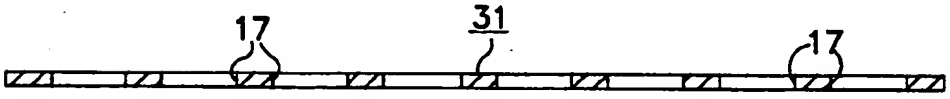


FIG. 12

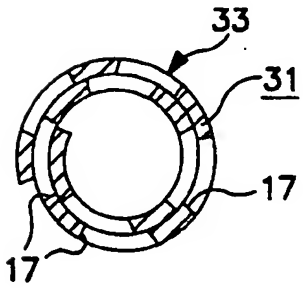


FIG. 13

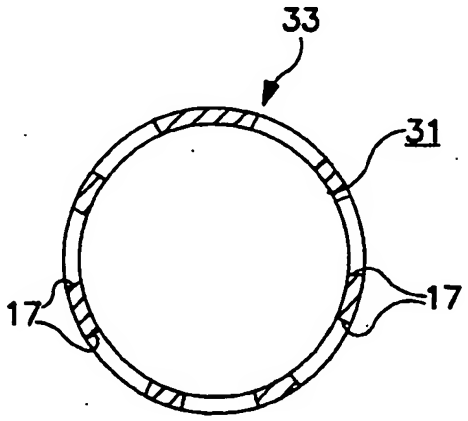


FIG. 14

MINIMALLY INVASIVE BIOACTIVATED ENDOPROSTHESIS FOR VESSEL REPAIR

This is a continuation of application Ser. No. 07/971,217 filed on Nov. 4, 1992 now abandoned.

FIELD OF THE INVENTION

The present invention relates to an improved percutaneously inserted endoprosthesis device which is permanently or temporarily implanted within a body vessel, typically a blood vessel. More particularly, the present invention relates to a new procedure for administering localized bioactive substances via prostheses designs which are adapted to resist problems associated with restenosis, thrombosis, infection calcification and/or fibrosis after implantation.

BACKGROUND OF THE INVENTION

In certain medical treatment procedures, a type of endoprosthesis device known as a stent is placed or implanted within a blood vessel for treating various problems such as stenonses, strictures, or aneurysms in the blood vessel. These devices are implanted within the vascular system to reinforce collapsing, partially occluded, weakened or abnormally dilated sections of the blood vessel. Stents may also be implanted in the ureter, urethra, bile duct, or any body vessel which has been narrowed, weakened or in any of the other ways which requires reinforcement.

A common approach for implanting stents in peripheral or coronary arteries is to first open the constricted region of the vessel via a percutaneous transluminally inserted angioplasty balloon catheter. The uninflated balloon at the tip of the catheter is advanced into the narrowed portion of the vessel lumen. The balloon is inflated so as to push the stenotic plaque outward, thereby enlarging the luminal diameter. Thereafter another catheter containing the stent is advanced to the region just enlarged by the balloon catheter and the stent is deployed. The catheter is withdrawn leaving the stent within the vessel.

The concept of implanting transluminally placed coil sprint stents within an artery is not new. In one experiment in 1969, six stents were implanted in arteries of dogs. Three stents were stainless steel covered with silicone rubber and the other three stents were bare stainless steel. All three silicone coated stents occluded within 24 hours while two of the three bare stents remained open for thirty months. The stents were deployed using a pusher catheter having the same outer diameter as the stent.

In 1983, thermally expandable stents were reported, in which an alloy wire was shaped at thigh temperature into a stent configuration. Later it was straightened at room temperature into a configuration suitable for transluminal placement. Once placed within the vessel the stent was exposed to elevated temperatures to cause the alloy to return to its initial coil configuration. Canine studies of these stents, using the alloy nitinol, an alloy of nickel and tantalum, demonstrated restenosis and intimal thickening 8 weeks following implant.

In 1984, self-expanding stents were described in which a device was introduced percutaneously after torsion reduction and was deployed by applying a reverse torsion in-vivo. This type of device proved to be complex and limited by a small expansion ration. Another self-expanding stent used stainless steel wire in a

zig zag configuration which resulted in incomplete vascular contact and only partial healing of the device. Yet another mechanical self-expanding stent was reported where a woven multifilliment stainless steel stent was deployed by a catheter with a constricting outer sleeve. Once in place, the outer sleeve was removed allowing self-expansion of the spring stent against the vessel wall.

Thrombosis occurred in these early prototypes, especially when the vessel tapered, and at branch points and at low expansion ratios. Canine aortic implantation resulted in multiple areas of vessel-to-stent adhesion at 3 weeks following implant. The stent exhibited minimal thrombogenicity.

Balloon expandable stents were first reported as being constructed of woven stainless steel wire where the cross points were silver soldered to resist radial collapse. The stent was deployed unexpanded over a balloon catheter, and once in position the stent was expanded by the outward force of the balloon. 8 of 11 stents implanted remained open for 1 to 8 weeks. It has been observed that the amount of intimal hyperplasia to be inversely proportional to the initial vessel lumen diameter. In another version, silver soldering cross points were replaced by the use of a stainless steel tube with rows of offset slots which became diamond shaped spaces. Although neointimal hyperplasia was observed, all stents remained open in rabbit aortas for 6 months.

Placement of a stent in a blood vessel is described in Lindemann et al U.S. Pat. No. 4,878,906 where a combination of sheath covered sleeve and a balloon catheter are used to locate and place the prosthesis. No recognition is given to the problems just discussed herein.

A prosthesis system using an expandable insert is shown in Garza et al U.S. Pat. No. 4,665,918, which is typical of those devices which are implanted without any express concern for the biocompatibility of the device being inserted. One can expect many of the foregoing problems and concerns to be evidenced by this device.

One device which is shown in U.S. Pat. No. 4,768,507 to Fischell et al describes a coil spring stent on which an application of a carbon coating or a carbon coated polytetrafluoroethylene has been applied on the surface of the coil spring. Fischell et al teaches that the thrombogenic potential of the device is reduced, through a passive methodology, but does nothing to address the biological response to the implant as a foreign body. Moreover, no suggestion is made of a way to inhibit neointimal hyperplasia, which inevitably follows balloon catheter induced injury to arterial vessels.

Yasuda U.S. Pat. No. 4,994,298 employs plasma polymerization to form a thin flexible coating on stents, teaching that improved biocompatibility, such as nonthrombogenicity and tissue or blood compatibility may be improved. Again this process is a passive methodology as previously described.

There are essentially two types of stents which have been employed in the prior art. Spring like stents have been inserted using a sheath or restraining element to keep the spring from expanding until it is in place. The other form of stent uses a method of expanding the stent once it is in place, such as a balloon catheter. Kreamer U.S. Pat. No. 4,740,207 describes one version of the balloon catheter version. In this patent, a semi-rigid tube which has a smaller relaxed diameter which is expanded to a larger operating diameter which is maintained by a retaining ledge on the inside of the graft.

Concern here, of course, is that the inside located ledge and other retaining means may inadvertently function to cause further blockage of the tube once it is installed. Also, Kreamer states that the tube is held in place by friction between the outer periphery of the graft and the inner periphery of the vessel to prevent displacement of the grant once in place in the vessel. The obvious concern is that the size must be precise or the tube will expand too much or too little, either damaging the vessel or escaping from the location for which it was intended.

Prior art devices represent a foreign body that has no biologically active properties and thus are a factor which contributes in a major way to the eventual restenosis or thrombosis of the vessel. These prior art devices attempt to reduce neointimal hyperplasia passively by adjusting mechanical variables such as lowering the stent profile, coating the stent with carbon, or by making the stent more or less rigid or flexible.

Accordingly, it is an object of the present invention to provide a device and method for deploying stents in blood vessels and other regions of the body without concern for the precise size of the stent being employed or the size of the vessel being treated or repaired.

It is an important object of this invention to produce a stent device and delivery system for the stent which produces rapid endothelialization with the least amount of intimal hyperplasia. While this goal has been stated by others, no effective method or device has been proposed to accomplish that goal.

Another object of this invention is to provide an endoprosthesis device and method for its use in which problems associated with restenosis, thrombosis, infection calcification and/or fibrosis after implantation may be avoided.

Yet another object of the present invention is to provide a device which is effective in administering localized bioactive substances to prevent rejection and side effects from an implanted endoprosthesis device.

Other objects will appear hereinafter.

SUMMARY OF THE INVENTION

It has now been discovered that the above and other objects of the present invention may be accomplished in the following manner. Specifically, an minimally invasive bioactivated endoprosthesis for vessel repair has been discovered which is admirably suited for long term use in a variety of surgical procedures and treatments.

The device is intended for use in those medical treatment procedures where a type of endoprosthesis device known as a stent is placed or implanted within a blood vessel for treating various problems such as stenonses, strictures, or aneurysms in the blood vessel. These devices may also be implanted within the vascular system to reinforce collapsing, partially occluded, weakened or abnormally dilated sections of the blood vessel. Stents of the present invention may also be implanted in the ureter, urethra, bile duct, or any body vessel which has been narrowed, weakened or in any of the other ways which requires reinforcement.

The device comprises a minimally invasive bioactivated endorposthesis device for vessel repair, including a stent which is formed from metal or polymers into a predetermined shape which includes a plurality of holes patterned with a desired size, shape and number to provide a desired bending modulus. The stent may be fabricated from stainless steel, nitinol or other appropriate metallic alloys or may be formed from a variety of polymers which are known to be suitable for use with the human body.

When a metallic stent is employed, it is formed and then coated with a polymer which contains a bioactive substance which achieves an equilibrium with the surrounding body tissues or fluids, with the equilibrium being controlled by charge distribution, concentration and molecular weight of the bioactive substance in relation to the pore size of the polymeric carrier. Among these polymers are polymers having a microporous structure, such as silicone, polyurethane, polyvinyl alcohol, polyethylene, biodegradable polylactic acid polymers, polyglycolic acid polymers, polyesters, hydrogels, tetrafluroethylene and polytetrafluroethylene, fluorosilicone and combinations, copolymers and blended mixtures thereof.

If the stent is formed from a polymer, these same polymeric materials may be employed, although some may need to be structurally reinforced. Also useful as a polymeric stent is polymethylmethacrylate, which is an example of the generic class of structurally adequate polymers without reinforcement.

A bioactive substance is preferably admixed in the polymer for elution from the microporous structure of the stent or coating on the stent after implantation. The rate of elution of the bioactive substance is controlled by selecting a pore size for the microporous structure in response to the concentration and molecular weight of the bioactive substance to achieve equilibrium between the polymer and the tissue or fluids proximate the stent upon implant. This permits a controlled and prolonged release of the bioactive substance.

The bioactive substance may be selected from the group of heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments.

The stent itself may take several distinct configurations, all of which have a predetermined biasing force acting on the diameter of the stent. A flat, rectangular strip of stent material is formed, with the size being determined by the size of the blood vessel or other body conduit where the stent will be placed. As previously set forth, the strip includes a plurality of holes patterned with a desired size, shape and number to provide a desired bending modulus. Locking tabs are provided to engage the some of the plurality of holes at the maximum expanded size to prevent return to the smaller diameter coiled shape.

Preferred is a rolled stent which is provided with a coiled shape to which it tends to return when expanded. This is accomplished by using the same edge of the strip on which the tabs are formed as a rotational axis to roll the strip into a tight coil so that the tabs are in the center of the coil. Heat is applied to cause the strip to take a set in this coiled shape, so that when the coiled strip is radially expanded or unrolled, the form stresses will bias the strip to roll back into the preferred shape. The tabs which have been formed on what is now the inside edge will engage the holes formed in the strip and prevent collapse to the biased shape. Since a plurality of holes are formed in the strip, the device may be expanded to different sizes, depending upon the particular vessel in which it is placed. Under some circumstances,

the device is capable of assuming a stent shape with more than one diameter, for the first time in these applications.

Alternatively the predetermined bias of the stent may be the expanded size so that the stent is coiled against this bias during insertion. Holes are still placed in the sheet or strip to encourage adoption of the stent by the vessel. However, the relaxed or unbiased position is that of the intended final shape, and therefore locking tabs are not necessary. The stent is compressed or rolled to a smaller diameter prior to use with a built in bias to return to the "in use" shape previously built into the stent. This embodiment is installed using an introducer sheath. A balloon catheter may or may not be needed in view of the built in bias.

BRIEF DESCRIPTION OF THE DRAWINGS

For a more complete understanding of the invention, reference is hereby made to the drawings, in which:

FIG. 1 is an isometric view of an endoprosthesis for vessel repair.

FIG. 2 is an isometric view of the device shown in FIG. 1 in the most fully opened position.

FIG. 3 is a sectional view taken on line 3,3 of FIG. 1.

FIG. 4 is a sectional view taken on line 4,4 of FIG. 2.

FIG. 5 is a plan view development of the endoprosthesis blank prior to formation.

FIG. 6 is an end view of the device of FIG. 5 as viewed from the left hand side.

FIG. 7 is a sectional view taken on line 7,7 of FIG. 5.

FIG. 8 is a plan view development of a second embodiment for an endoprosthesis blank.

FIG. 9 is a sectional view taken on line 9,9 of FIG. 8.

FIG. 10 is a sectional view similar to FIG. 4 but showing the endoprosthesis formed from the blank of FIG. 8

FIG. 11 is a plan view development of a third embodiment for an endoprosthesis blank.

FIG. 12 is a sectional view taken along line 12,12 of FIG. 11.

FIG. 13 is a sectional view similar to FIG. 4 but showing the endoprosthesis formed from the blank of FIG. 11.

FIG. 14 is a view of the endoprosthesis of FIG. 13 after insertion and expansion in its position of intended use.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

As shown in the drawings, the device of this invention comprises a minimally invasive bioactivated endoprosthesis device, 10 generally, for vessel repair in contact with surrounding body tissues or fluids. The device includes a stent 11 which may be installed in the vessel using a catheter 13, and in some cases using a balloon 15 on the end of catheter 13. Stent 11, which contains a plurality of holes 17, is shown in a tightly coiled pre-insertion position in FIG. 1 with a fragment of balloon catheter 13 shown about to be inserted medially within the endoprosthesis. The sectional view shown in FIG. 3 illustrates a tab 19 which does not engage any holes 17 and which is enclosed within the coiled stent 11, as the stent is in its relaxed or steady state with no bias from external forces acting on the stent.

In FIG. 2, the stent 11 is illustrated in its most fully opened and locked position, as expansion has been effected diametrically by means of the medially positioned balloon 13. FIGS. 2 and 4 shows how the tab 19 engage holes 17 and prevent the stent from re-coiling upon itself to return to the position shown in FIG. 3.

The direction of the catheter and the balloon define an axis for reference to the various stents shown herein as part of the present invention. FIG. 5 is a plan view development prior to tightening and assembly of the stent into the predetermined shape. The stent 11 comprises a flat, rectangular strip 21 of a size determined by the size of the blood vessel or other body conduit where stent 11 will be placed. Tabs 19 extend along one end of strip 21 and are angled, as shown in FIG. 7. Strip 21 is coiled and biased to take a smaller diameter coiled shape, as tabs 19 engage some of the plurality of holes 17 at a maximum desired expanded size to prevent return to the smaller diameter coiled shape.

The coiled stent 11 is formed by using that edge of strip 21 on which the tabs 19 are formed as a rotational axis to roll the strip 21 into a tight coiled stent so that the tabs 19 are in the center so that when coiled strip 11 is radially unrolled to the position shown in FIG. 2, the form stresses will bias the strip 21 to roll back into the preferred shape of FIG. 3, and tabs 19 will engage holes 17 formed in strip 21, so as to prevent collapse to the biased shape of FIG. 3.

By using the same edge of the strip 21 on which the tabs 19 are formed as a rotational axis to roll the strip into a tight coil, tabs 19 are in the center of the coiled stent. Heat is applied to cause the strip to take a set in this coiled shape, so that when the coiled strip is radially expanded or unrolled, the form stresses will bias the strip to roll back into the preferred shape. Tabs 19 which have been formed on what is now the inside edge will engage the holes 17 formed in the strip and prevent collapse to the biased shape. Since a plurality of holes 17 are formed in the strip 21, the device may be expanded to different sizes, depending upon the particular vessel in which it is placed. Under some circumstances, the device is capable of assuming a stent shape with more than one diameter.

A slightly different stent layout is shown in FIGS. 8–10, in that tabs 19 are replaced with pointed tabs 20. Again the coiled stent 11 is heated or otherwise biased to move to a collapsed or tightly coiled condition. Pointed tabs 20 engage holes 17 and prevent such re-coiling. In addition, pointed tabs 20 engage the side walls of the blood vessel or other part of the anatomy where the stent has been deployed.

Turning now to FIGS. 11–14, an alternative embodiment is shown in which a strip 31 is formed into the desired size and shape, with holes 17 being provided for flexibility and for engagement with the tissue after implantation in some instances. No tabs are needed for this embodiment since this stent will have an outward biasing tendency. The stent assumes the shape shown in FIG. 14 after heating or otherwise forming the rolled stent into a usable configuration. When implantation is desired, the stent 33 is constricted to a smaller diameter as shown in FIG. 13, so that the bias of the design is to expand the stent. An introducter sheath of the type already in use should be used to position the stent in the vessel of choice. It may be only necessary to pull the sheath back to expose the stent.

In all of the devices of this invention, it is intended that a polymer form the exterior surface of the stent, either as a coating or as the stent itself. The drawings should be interpreted to understand that a polymer does form the exterior surface, whether or not a substrate

such as a metal stent is used. The polymer should have a microporous structure with a predetermined pore size. Also included in the polymer is a bioactive substance having a charge distribution, concentration and molecular weight selected which achieves an equilibrium in relation to the pore size of the polymeric carrier with said surrounding body tissues or fluids.

Among these polymers are polymers having a microporous structure, such as silicone, polyurethane, polyvinyl alcohol, polyethylene, polyesters, hydrogels, tetrafluroethylene and polytetrafluroethylene, fluorosilicone and combinations, copolymers and blended mixtures thereof. One preferred resorbable polymer is biodegradable polylactic acid, and another is polyglycolic acid. These materials are suitable for being formed into a stent that possesses acceptable tensile strength characteristics.

If the stent is formed from a polymer, these same polymeric materials may be employed, although some may need to be structurally reinforced. Also useful as a polymeric stent is polymethylmethacrylate, which is an example of the generic class of polymers having good structural properties. In any event, the bioactive substance is incorporated into the polymer prior to insertion of the stent into the vessel.

Radio opaque substances such as, for example, fluorescein, may also be incorporated into the stent so as to assist in the deployment and subsequent evaluative follow-up of the surgery. A primary purpose of the bioactive substance is to inhibit vessel wall restenosis following vascular balloon angioplasty. In addition, stents of the present invention may be used to improve the diameter of the urethra or fallopian tubes.

Preferred bioactive substances are heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments. Of course, virtually any bioactive substance of need to the patient is a possible agent for treating the patient, depending upon the needs of the treatment.

The preparation of the stents of this invention is as follows. When a metallic stent is contemplated, and any of these stent designs may benefit from the concepts of this invention, a medical grade of polymer is selected. Preferred is a silastic elastomer. A quantity of silastic elastomer is mixed in a 3 to 1 ration with ethyl ether to form a solution suitable for coating a metallic stent. A quantity of bioactive substance required to achieve the desired therapeutic effect is admixed with the polymer and ethyl ether solution. After thorough blending, the now bioactivated polymer solution is ready to be used to coat the stent.

The cleaned metallic stent is coated by the bioactivated polymer using a variety of methods. One method is to completely submerge or dip the stent into a quantity of polymer so that the metallic stent is fully covered. After coating and removing from the dip, the polymer is cured or vulcanized at the desired temperature, depending upon the polymer. Alternatively, the polymer may be sprayed on to the polymer and then cured. Yet another method includes pouring a coating over the stent while the stent is being rotated. Plasma coating is also effective.

While particular embodiments of the present invention have been illustrated and described, it is not intended to limit the invention, except as defined by the following claims.

I claim:

1. A minimally invasive bioactivated endoprosthesis device for vessel repair in contact with surrounding body tissues, comprising:

a stent formed from a flat sheet having an appreciable width to thickness to present a substantial surface to said tissues and coiled to a size for use with a blood vessel or other body conduit and including a plurality of holes, said holes being sufficiently large to permit rapid endothelialization, said stent further including at least one tab for cooperative engagement with said holes to form an internally unrestricted stent having a diameter adjusted to a selected size for said blood vessel or other body conduit; and

a polymer forming the exterior surface of said stent for operative contact with said tissue, said polymer having a microporous structure with a predetermined pore size and further including a bioactive substance within said pores for elution from said pores, said pore size being selected in response to the concentration and molecular weight of said substance to achieve equilibrium between said polymer and said tissue to provide a controlled and prolonged release of said bioactive substance to said surrounding body tissue in an amount sufficient to substantially prevent hyperplasia or therapeutically treat said tissue, said stent having a sufficient amount of said substantial surface to support a quantity of said polymer capable of prolonged release of said amount.

2. The device of claim 1, wherein said stent comprises a flat, rectangular strip of stent material sized by the size of the blood vessel or other body conduit where the stent will be placed and biased to take a smaller diameter coiled shape, said strip having locking tabs along one edge for engaging some of the plurality of holes at a maximum desired expanded size to prevent return to the smaller diameter coiled shape.

3. The device of claim 2, wherein said coiled stent is formed by using said edge of said strip on which the tabs are formed as a rotational axis to roll the strip into a tight coil so that the tabs are in the center of said coil so that when said coiled strip is radially unrolled, the form stresses will bias the strip to roll back into the preferred shape and said tab engage said holes formed in said strip to prevent collapse to the biased shape.

4. The device of claim 3 in which said stent is expanded to different selected sizes, depending upon the particular vessel in which it is placed.

5. The device of claim 4, wherein said coiled shape is adapted to assume a stent shape with more than one diameter.

6. The device of claim 1, in which said predetermined shape includes a predetermined bias of said stent to an expanded size such that the unbiased position is that of the intended final shape.

7. The device of claim 6 wherein said stent is compressed to a smaller diameter prior to use with said predetermined bias urging return to the predetermined shape.

8. The device of claim 1, wherein said stent comprises a metallic strip having a polymer coating.

9. The device of claim 8 wherein said polymer is selected from the group of silicone, polyurethane, polyvinyl alcohol, polyethylene, biodegradable polylactic

acid polymers, polyglycolic acid polymers, polyesters, hydrogels, tetrafluroethylene and polytetrafluroethylene, fluorosilicone and combinations, copolymers and blended mixtures thereof.

10. The device of claim 9 wherein said stent is formed from a polymer.

11. The device of claim 10 wherein said polymer has sufficient structural integrity to be formed into a stent.

12. The device of claim 11 wherein said polymer is polymethylmethacrylate.

13. The device of claim 1, wherein said bioactive substance is selected from the group of heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein byproducts, antifibrosis agents, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments.

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